A THESIS ENTITLED

"REACTIVITY AND ASPECTS OF THE N.M.R. SPECTROSCOPY OF BICYCLIC COMPOUNDS."

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DEDICATED

TO

FLORENCE

CONTENTS

SUMMARY

A series of novel 4-substituted camphors has been synthesised and fully characterised. Their ^{13}C spectra have been determined and augment a study carried out previously, on a restricted range of substituents, to correlate the substituent parameter σ_I with the carbonyl carbon chemical shift. Electron releasing substituents (ylids) have been included in the present survey and their σ_I value estimated by extrapolation from a Hammett type plot.

Hammett $\rho\sigma$ analysis has also been applied to data obtained from the sodium borohydride reduction of a series of 4-substituted camphors, in an attempt to understand more fully the mechanism of this common reaction. The kinetic results are in agreement with the findings of other studies and a rationale of the observed substituent effects is proposed in light of the Hammett analysis and the known electronic environment at the carbonyl carbon of the variously substituted camphors.

The kinetics of the gas phase pyrolysis of a series of 4-substituted isobornyl acetates have been studied and consequently, valuable experimental data pertaining to the controversial β-substituent effect obtained. The present results are in accord with long standing postulates but put in some doubt recently published theories regarding this much disputed subject.

In an effort to synthesise the target molecule, 4-methoxy camphor, photolysis reactions on iodo-bornane derivatives were attempted; with most substrates, the photo-products obtained could

be explained in terms of analogous reactions of norbornyl and cyclohexyl derivatives and their subsequent products. However, in a few examples, Wagner-Meerwein rearrangements were envisaged as partly responsible for the isolated products.

Intrinsic anisochrony induced by the transmission of chirality across an acetylene linkage was detected in a series of substituted 4-ethynyl camphors; both the alcohol and acetate derivatives exhibited splitting in the ^{13}C spectrum but in contrast the methyl ether did not.

A study has been made of the reaction of highly unreactive bridgehead iodides with meta-chloro perbenzoic acid and as a result of this work the first saturated iodoso dicarboxylate has been prepared.

INTRODUCTION

PART I

^{13}C N.M.R. SPECTROSCOPY[1,2,3]

Nuclear magnetic resonance was first observed by Rabi and his co-workers[4] in 1939, but little interest was generated in the chemical world regarding this topic until 1949, when it was discovered that the exact resonance condition for a given type of nucleus depends upon its chemical environment.[5] By 1951, the term "chemical shift" had been coined to describe the differences in resonance conditions required for the same isotope in different chemical environments.[6] With this discovery, N.M.R. became tremendously important for chemists as a new method for the study of molecular structure. Since then, proton N.M.R. spectroscopy has been applied to a wide variety of chemical problems ranging from structural and stereochemical determination to kinetics. With the advent of more advanced experimental techniques (in particular pulse methods) the fundamental problem of low sensitivity of ^{13}C nuclei, associated with a small magnetic moment and low natural abundance, has been overcome, and this offers the organic chemist an alternative investigative tool which has distinct advantages over ^{1}H N.M.R. The range of ^{13}C shieldings in neutral and charged organic compounds[7] is in excess of 600 p.p.m., compared with 20 p.p.m. for protons. The use of a decoupling technique which eliminates spin-spin interactions of ^{13}C nuclei with neighbouring magnetic nuclei (normally protons), in conjunction with the large chemical shift range, enables the assignment of specific signals to the various

non-equivalent carbons. Furthermore, direct investigation of the carbon skeleton is feasible for, in particular, non-protonated moieties such as carbonyls and nitriles.

THE N.M.R. EXPERIMENT

Unlike the properties of charge and mass, angular momentum and hence magnetic moments are possessed only by some of the atomic nuclei. Those that do may be considered as spinning bodies. Nuclei with odd mass numbers have nuclear spins whose value I, is an odd-integral multiple of $\frac{1}{2}$. The angular momentum may be expressed in terms of the magnetic moment μ as :-

$$\mu = \gamma \frac{I\,h}{2\,\pi}$$

where h is Planck's constant and γ is the magnetogyric ratio, a constant for the particular nucleus under study. The maximum observable component of the angular momentum is I, the spin quantum number, and the permitted values of the vector moment along any specific axis, are given in terms of the magnetic quantum number m, as a series :-

$$m = I, (I - 1), (I - 2), \ldots\ldots\ldots, -I$$

Therefore, the number of spin states for a nucleus is dictated by its spin quantum number such that for a nucleus, spin I, the number of possible orientations is $2I + 1$. These states are degenerate in the absence of a magnetic field but, in the presence of an applied field, these correspond to different potential energy levels. When

$I = \frac{1}{2}$, as is the case for ^{1}H and ^{13}C, two energy states are produced, corresponding to alignment with and against the field. The N.M.R. experiment is the detection and measurement of transitions between these states.

In a magnetic field H_o, a magnetic moment, μ , lies at an angle θ with respect to the field axis (z axis fig. 1). The interaction of H_o and μ causes a torque, which tips μ towards H_o but due to the nuclear spin this causes the nucleus to precess about the z axis and θ does not change. This is analogous to the situation of a top spinning in the gravitational field of the earth. The frequency of precession, ν_o, is given by the Larmor equation :-

$$\nu_o = \frac{\gamma H_o}{2\pi}$$

which is independent of θ.

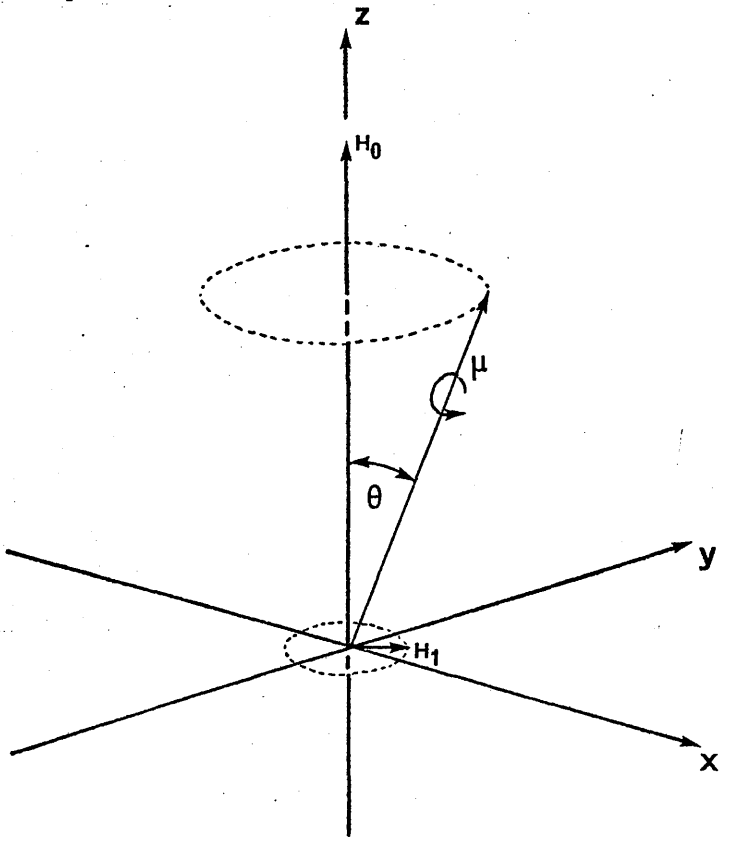


Figure 1.

If a small rotating field, H_1, of frequency ν_o, is generated at right angles to H_o, μ experiences the combined effects of H_o and H_1. Under these conditions, the nucleus can absorb energy from H_1 and θ changes. When the magnetic component of H_1 induces transitions between the two energy levels, the resonance condition is reached.

An expression to show the interaction of H_o and μ has been formulated :-

$$h\nu = \frac{H_o}{I} = \Delta E$$

where ΔE is the difference in energy between adjacent nuclear spin states (fig.2).

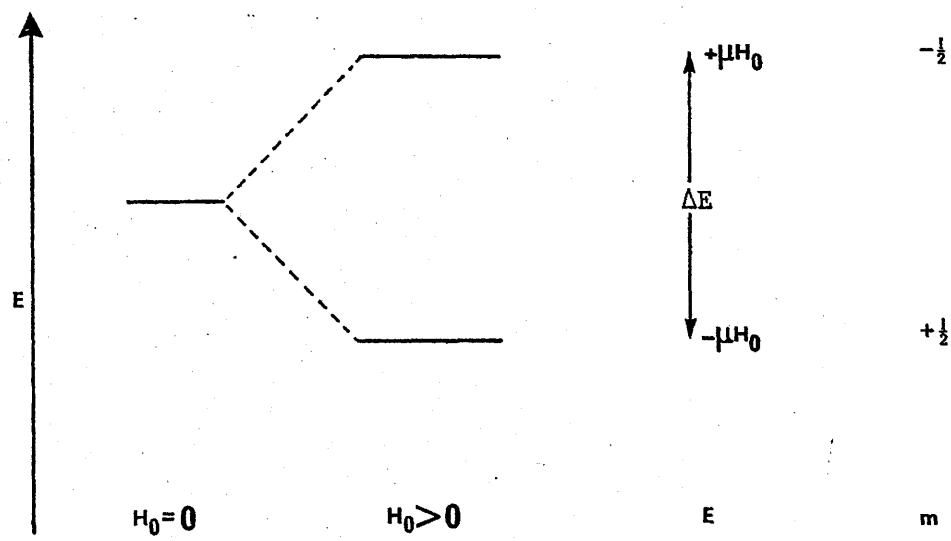


Figure 2.

For ^{1}H and ^{13}C nuclei whose I value is $\frac{1}{2}$, only two energy states are allowed by quantum mechanical theory and these are different by an amount $2 \mu H_o$. The population distribution between the two states is given by the Boltzmann equation :-

$$\frac{N_+}{N_-} = \exp \frac{-\Delta E}{kT}$$

where N_+ and N_- are the populations of the upper and lower states respectively. At equilibrium, the excess population in the lower state is given by :-

$$N_{eq} = \frac{(N_- - N_+)}{N_-} \approx \frac{2 \mu H_o}{kT}$$

The application of an appropriate oscillating electromagnetic field of frequency ν_o on the already magnetically polarised nuclei will induce transitions between the unequally populated energy levels. The probability of the excitation frequency ν_o causing a transition from the lower to upper state is exactly equal to the probability of the reverse process. However, because there are more nuclei in the lower energy state, a net absorption will occur. N.M.R. experiments achieve maximum perturbation of the energy levels by utilising a slow sweep rate which requires that H_1 pass slowly through the resonance condition. Under these circumstances, the excess population in the lower level will diminish, while the upper level's population will increase until they become equal and no net absorption occurs. This phenomenon is known as saturation and if it were not for the fact that processes exist which exchange energy between the spin system (collection of

nuclei) and its surroundings and tend to re-establish the Boltzmann equilibrium, then the N.M.R. experiment would be of little value; these restoring phenomena are known as relaxation and provide a continuous supply of nuclei in the lower energy level.

NUCLEAR SPIN RELAXATION

In N.M.R., the transition between the energy levels involves such a small energy difference that the probability of spontaneous emission is negligible and therefore the excited nuclei depend on other radiationless mechanisms to return to their ground state. Transitions are induced through an interaction between the excited nuclei and their surroundings (known as the lattice). The thermal noise spectrum of a liquid structure or solid lattice is considered to be composed of rotational, translational and other degrees of freedom of the molecular system; some of these have appropriate radiofrequency components and may effect transitions analogous to the applied excitation frequency ν_o, but with the aim of restoring the Boltzmann distribution instead of destroying it.[8] Two different relaxation mechanisms may be considered, both of which are effectively first-order rate processes characterised by their own time constant; spin-lattice relaxation with time constant T_1 takes place because there is an energy exchange between the nuclear spin states and the surrounding medium, and spin-spin relaxation, of time constant T_2 occurs with similar exchange of energy but between different nuclear spins.

The rate of spin-lattice relaxation is dependent upon temperature, concentration of magnetic nuclei and viscosity of the medium. The characteristic "relaxation time" T_1 is the mean lifetime of the excess of nuclei in the non-relaxed state or, alternatively, it is the time required for the induced magnetisation to decay to its equilibrium value in the direction of H_o, the field axis and hence termed the "longitudinal relaxation time". In order to have efficient relaxation, it is necessary to have physical interactions which couple the array of nuclei to the lattice; there are several different processes but all occur through fluctuating, localised electric or magnetic fields derived from molecular motions. The most important of these are :-

(a) Magnetic dipole - dipole interactions (i.e. between the nucleus in question and other spin $\frac{1}{2}$ nuclei, or spins of unpaired electrons).

(b) Chemical shift anisotropy interactions.

(c) Scalar - coupling interations (for nuclei with spin $I > \frac{1}{2}$).

(d) Spin - Rotation interactions.

For ^{13}C nuclei bonded to hydrogen the first of these mechanisms dominates. The dipole - dipole interaction is caused by local magnetic fields associated with other spin nuclei or unpaired electrons in the neighbourhood of the excited nucleus. The said nucleus, in a magnetic field of H_o, experiences a net magnetic induction of H_o, plus a contribution from the local magnetic fields of neighbouring spins. In a fluid the orientations of all these spins are constantly changing with respect to H_o as a result of

rapid molecular motions (tumbling, internal rotations) and hence the total magnetic field experienced by the observing nucleus fluctuates. Such time-dependent fluctuations may have Fourier components of a frequency suitable to induce relaxation of the nucleus.

Since dipole - dipole interactions are proportional to the square of the magnetogyric ratio, of both couple nuclei and also inversely related to the sixth power of the distance between them, it is the common relaxation mechanism for proton-bearing carbons because of short C——H internuclear distances and the high magnetogyric ratio of the proton.

A prerequisite for efficient relaxations is that molecular motions have a suitable time scale, since fluctuations that occur much more rapidly than the N.M.R. frequencies (10^7 - 10^8 Hz) have little effect. These frequencies, which are relatively low, correspond with translation and rotation of molecules in a liquid medium, and therefore it is these molecular motions which give rise to the appropriate Larmor frequency. It is unnecessary to consider separation of individual molecular motions such as rotation or tumbling, but it is more convenient to define these motions in terms of an effective correlation time τ_c, which is the time taken for a molecule to rotate through one radian.

Relaxation is best effected by rotational motions with frequencies comparable to the Larmor frequency of a given nucleus; for a ^{13}C nucleus in an applied magnetic field of 23.5 kG this is 2.5×10^7 Hz or ca 1.6×10^8 rad. sec^{-1}. This corresponds to a

correlation time of 7×10^{-9} s. The effect of τ_c on T_1 (and T_2) is shown in fig. 3.

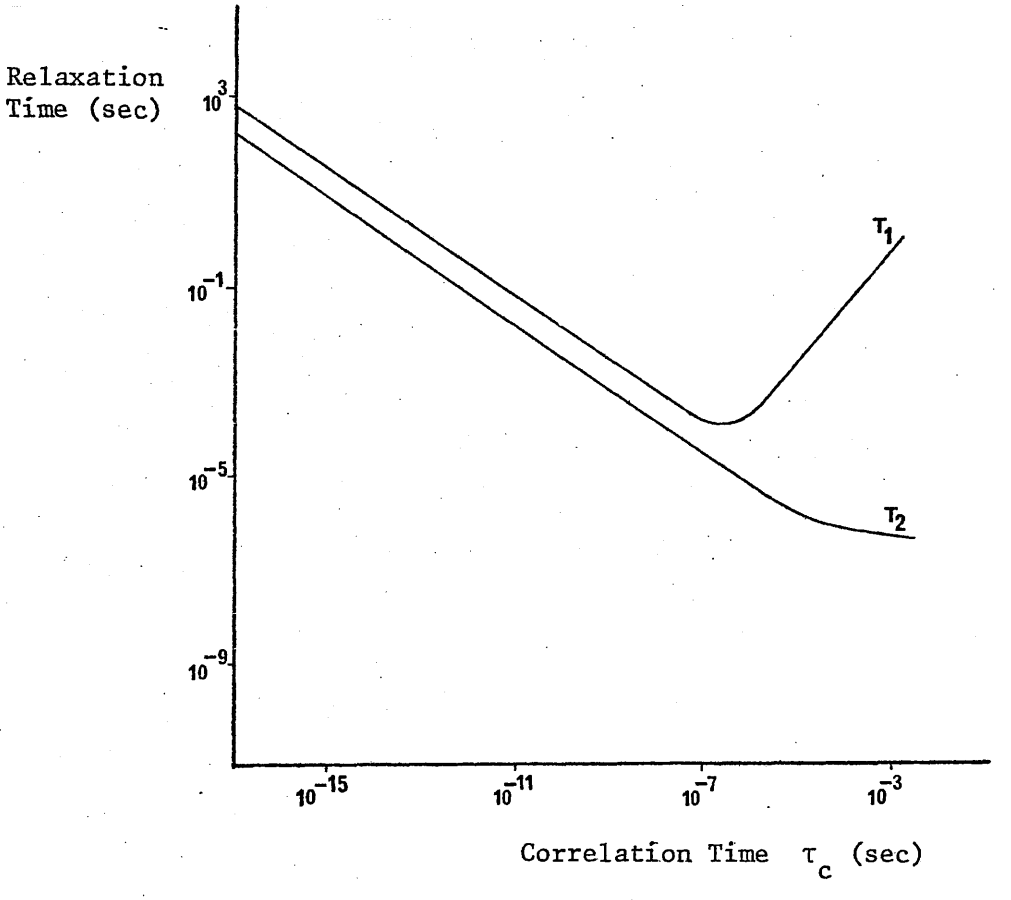


Figure 3.

The τ_c values for most molecules are below 10^{-9} s; typically correlation times of small molecules are in the range 10^{-12} - 10^{-13} s, but larger organic molecules (e.g. steroids) may have τ_c values as long as 10^{-10} s. Such molecules (molecular weight > 300) tumble relatively slowly in solution due to their size and interactions with solvent molecules. From fig.3, it is clear that in the region $\tau_c < 10^{-8}$ sec., T_1 increases as τ_c

decreases, whereas when $\tau_c > 10^{-8}$ sec., T_1 increases with τ_c. Hence, slower tumbling large molecules will relax more effectively than smaller molecules since they have correlation times closer to the optimum value for relaxation.

Chemical shift anisotropy is normally a rare contributor to the overall spin - lattice relaxation mechanism. This phenomenon arises from directional differences in the electronic environment of the nucleus which will produce rapid fluctuations of the effective magnetic field as the molecule tumbles in solution. The time constant T_1 due to chemical shift anisotropy is directly proportional to the square of the magnetic field strength and it follows that for most systems the process is of little significance unless large applied fields are employed (superconducting systems). Two examples where this mechanism plays an important role in the relaxation process, even at low H_o values, are the carbons marked * in Ph-C≡C-*C≡C-Ph and CH_3-*COOH.

Spin - spin relaxation, which will be dealt with later, involves coupling between nuclei of spin $\frac{1}{2}$; however, if such a nucleus is spin - spin coupled to a nucleus of spin greater than $\frac{1}{2}$, then scalar relaxation may occur. The prerequisite for such a process to take place is that the lifetime of spin states associated with the nucleus, spin $I > \frac{1}{2}$, is short compared with that of the nucleus whose resonance is being studied (i.e. it is undergoing rapid spin - lattice relaxation). Under such conditions, the local field due to the magnetism of the rapidly relaxing nucleus fluctuates and may induce

relaxation in the coupled nucleus. This mechanism is important for nuclei in the neighbourhood of quadrupolar nuclei which, because they possess spin greater than $\frac{1}{2}$ in an unsymmetrical environment, have short T_1 values. An example of this is the carbon directly attached to bromine in bromobenzene.

The mechanism of spin - rotation relaxation involves quantum rotational states of the molecule or of small symmetrical groups undergoing rapid internal rotation (e.g. methyl groups in a large molecule such as a steroid). For protonated carbons, this process competes with dipole - dipole relaxation and is the major contributor to T_1 for non-protonated small molecules such as carbon disulphide. The effect of higher temperatures is to make spin - rotation relaxation more efficient (i.e. shorter T_1) which is the inverse of the dipole - dipole situation.

Instead of exchanging energy between the spin system and an external sink (the lattice), spin - spin relaxation involves the transfer of energy within the spin system. Relaxations occurring by this mechanism are characterised by the "transverse relaxation time", T_2, so called because it is the time constant for the exponential decay of magnetisation in the plane perpendicular to the field axis (fig.4).

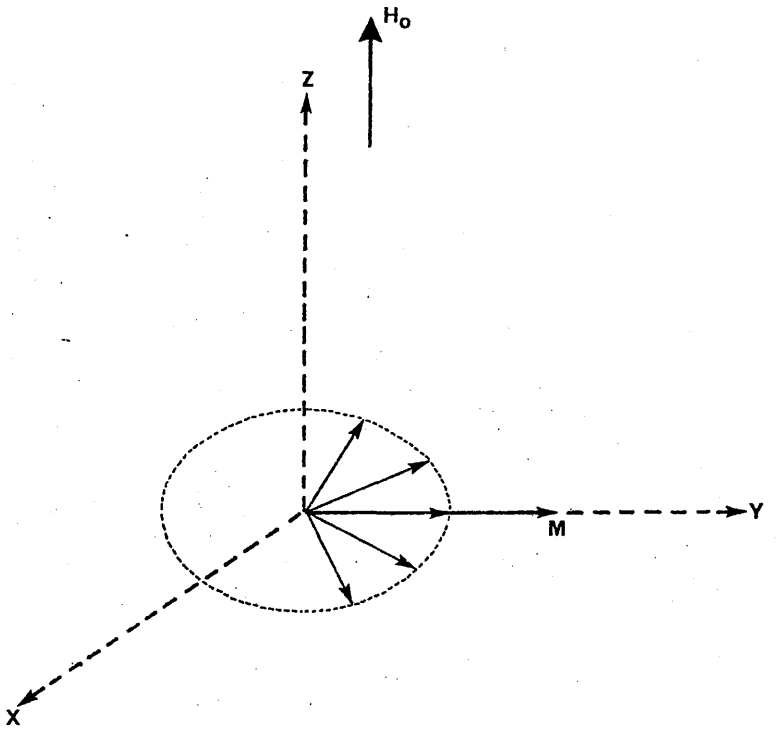


Figure 4.

Spin - spin (transverse) relaxation is caused by time-dependent magnetic or electric field at the nucleus in a similar manner to spin - lattice (longitudinal) relaxation. This arises from the interaction of neighbouring magnetic dipoles. Two conditions to be met before such a process can take place are :-

1) Close proximity to one another in space,
2) The nuclei must be identical.

Clearly this mechanism is closely related to the scalar relaxation process described for spin - lattice interactions. Consider two nuclei precessing about H_o. The precessing moment of each nuclei comprises of two components, (fig.5) - (a) is static and aligned with the field, and (b) is a rotating component in the XY plane. If

(b) is rotating at the Larmor frequency of the adjacent nucleus then it can induce a spin transition and the net effect would be simultaneous re-orientation of both nuclei with conservation of energy between the pair. This process affects the lifetimes of the nuclear spin states and in consequence causes line broadening.

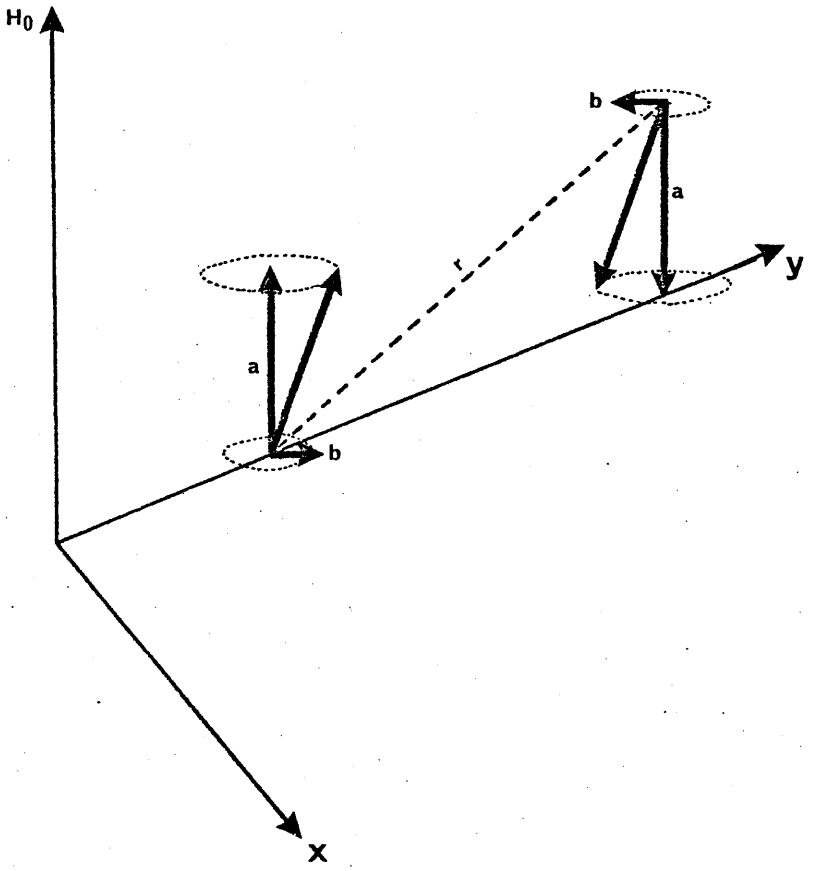


Figure 5.

FOURIER TRANSFORM N.M.R.

The sensitivity of the N.M.R. experiment to ^{13}C nuclei is impaired in comparison to ^{1}H nuclei, for two reasons :-

a) ^{13}C is only 1.1% naturally abundant while ^{1}H is almost 100% abundant.

b) The magnetogyric ratio of ^{13}C is $\frac{1}{4}$ that of ^{1}H and since the sensitivity of a nucleus is proportional to γ^{3}, a ^{13}C nucleus gives rise to $\frac{1}{64}$ of the signal intensity that a proton would generate.

The combined effect of these two factors results in a ^{13}C N.M.R. experiment which is less sensitive by a factor of nearly 6000 relative to proton N.M.R. This is particularly detrimental when the experiment is run on an earlier type of spectrometer, scanning by the continuous wave method (c.w.), which involves the observation of only one frequency at a given time. A partial solution to the sensitivity problem is the use of a rapid sweep method, which allows the use of more r.f. power, but no great enhancement of signal to noise ratio (S/N) results, and resolution is limited. The introduction of Fourier Transform (F.T.) N.M.R. has overcome the sensitivity and related problems, and allowed ^{13}C N.M.R. spectroscopy to become a practical complement to proton N.M.R.

In this form of N.M.R., the sample is subjected to a single short r.f. pulse of sufficient power and bandwidth to cause simultaneous excitation of all the transitions. The time domain spectrum obtained is a free induction decay (F.I.D.) and represents the simultaneous reradiation of all the frequencies absorbed by the various nuclei in the sample. For a single nucleus absorbing at one frequency, the F.I.D. is an exponentially decaying sine wave.

However, if the sample as a whole is considered, the F.I.D. is no longer a simple exponential decay, but is an interferogram made up of all the resonance absorption frequencies. By using a Fourier Transformation (F.T.) it is possible to convert the spectral information from the time domain into the frequency domain, which results in a frequency absorption spectrum identical with that which would be produced by c.w. scanning. The lifetime of the individual frequency components defines the resolution (linewidths in Hz); those that decay rapidly correspond to broad lines, whereas those that decay slowly, to sharp lines. The sensitivity improvement for a single pulse experiment over c.w. N.M.R. is, in theory, over 100 but, in practice, about 10. Both methods use time averaging techniques in order to improve signal to noise ratio (S/N). It takes the same time to make several thousand 50 - 250 sec. c.w. scans as it does to record ca 10^6 pulses, spaced 0.1 to several seconds apart. Since S/N ratio is proportional to the square root of the number of scans or pulses, a shorter period of time is required to achieve a given S/N enhancement for F.T. N.M.R. The time improvement created by the pulse experiment is >100.

^{1}H DECOUPLING AND NUCLEAR OVERHAUSER EFFECT

Often, ^{13}C spectra are difficult to interpret because of fine structure on resonance lines which arises from the phenomenon of spin - spin coupling; this may be due to interaction with a directly attached proton ($J > 125$ Hz) or with more remote nuclei,

two to four bonds distant ($J < 20$ Hz). The multiplicity of the lines may be simplified by application of wide-band proton noise decoupling which involves simultaneous irradiation of all protons in the sample. This has the effect not only of cancelling $^{13}C - {}^{1}H$ spin - spin coupling but also creates an enhancement of signal. This enhancement results from two factors; one is the simplification of the spectrum and the other is the Nuclear Overhauser Effect (N.O.E.).

The Nuclear Overhauser Effect is a result of disruption of the upper and lower energy level populations when proton decoupling takes place. For ^{13}C nuclei the dominant relaxation process is dipole - dipole interaction with neighbouring protons and if these are being irradiated, the net effect is to bring about more efficient relaxation and hence at equilibrium, an excess population (over the Boltzmann distribution) exists in the lower carbon energy level. In such a situation, more carbon nuclei are in a position to be excited and hence more transitions occur with an attendant enhancement of signal. The N.O.E. enhancement has a maximum of 2.988 for ^{13}C, which means that each carbon resonance will have a peak area up to 2.988 times the total resonance signal area in the absence of proton irradiation. This optimum value is normally obtained for protonated carbons in molecules of molecular weight > 150.

For ^{13}C decoupled spectra, as described, there is no direct correlation between the integrated peak areas and the number of ^{13}C nuclei in each peak. There are two reasons for this, differential Nuclear Overhauser Enhancements and long spin - lattice relaxation times. In the pulse experiment, due to insufficient time between

pulses, many nuclei are unable to relax fully and give rise to spectral lines with spurious integrations. Although the pulse repetition rate is of the order of 0.1 - 1 sec. and relaxation times are larger than 0.1 - 0.2 sec., the system requires times $\sim 5\ T_1$, in order to relax sufficiently. Therefore, many nuclei have not reached thermal equilibrium before another pulse is applied, and with a smaller excess of nuclei in the lower energy level, fewer transitions occur giving rise to less intense resonances. Slower pulse rates allow the nuclei time to relax fully, but variable N.O.E. for different types of carbon still prevent valid integrations to be made.

Although wide-band decoupling is a useful technique in simplifying the otherwise complex ^{13}C spectrum, it does have the disadvantage of destroying all $^{13}C - {}^{1}H$ spin - spin coupling. This can be overcome by using single frequency off-resonance decoupling which retains directly bonded carbon - hydrogen spin - spin coupling information but removes long range coupling. Quaternary, methine, methylene and methyl carbons are observed as singlets, doublets, triplets and quartets respectively which makes assignment of individual resonances more facile. The coupling observed in the off-resonance experiment is not the true J_{C-H}, but the residual coupling, J_R, given by the formula :-

$$J_R = \frac{J_{C-H}^{x}\ \delta z}{\frac{\gamma H_2}{2\pi}}$$

where J_R = spin - spin coupling observed,

J_{C-H} = true spin - spin coupling,

δ_z = distance in Hz of the centre frequency of proton irradiation from the signal being decoupled,

$\frac{\gamma H_2}{2\pi}$ = radio frequency power of decoupling.

Homonuclear decoupling, employed in proton spectra is occasionally useful in assigning ^{13}C nuclei. If, using proton spectra, the resonance frequencies of protons coupled to specific carbons can be recognised, then low power irradiation of these protons in the ^{13}C experiment will result in collapse of the signal for the carbon bearing protons to a singlet and leave the uncoupled carbons' multiplets unchanged.

PULSE METHODS : THE ROTATING FRAME OF REFERENCE

N.M.R. spectrometers designed to study low-sensitivity nuclei such as ^{13}C and ^{15}N often subject the spin system to a series of equally spaced pulses of r.f. energy. The experiment studies the decay of magnetisation of the sample as a function of time in between pulses and, in order to simplify the motion of the magnetisation, the rotating frame of reference is used. The co-ordinate system rotates about H_o in the same direction as that of precession of the nuclear moments and therefore H_1, the r.f. energy, is fixed in this frame of reference. When the sample is placed in a magnetic field, H_o, a net magnetisation, M_o aligned with the field axis (fig.6(a)) results. When the sample is irradiated by H_1 along the x-axis in the rotating frame, this turns M out of alignment

with H_o and toward the y axis (fig.6(b)). The length of the irradiation pulse determines how far M tips away from the z-axis. The time required to tip M through 90^o must be experimentally determined. If this time, the pulse width, is doubled then the magnetisation tips through 180^o (fig.6(c)). Such a pulse applied to a fully relaxed system causes a Boltzmann excess to form in the upper energy level and is known as a negative spin temperature. Since the N.M.R. spectrometer detects signals in the x y plane only no signal is detected after a 180^o pulse although spin - lattice relaxation (T_1) is occurring ((c) → (d) → (e) → (a) fig. 6). However, after a 90^o pulse M lies in the x y plane and T_1 and T_2 (spin - spin relaxation) occur and a signal is observed. Both relaxations occur simultaneously; longitudinal along the z axis and transverse in the x y plane as M moves back toward M_o. The x y magnetisation dephases towards zero as a function of T_2 and no further signal is observed when dephasing is complete even if relaxation along the z axis is not complete, as occurs when $T_1 > T_2$.

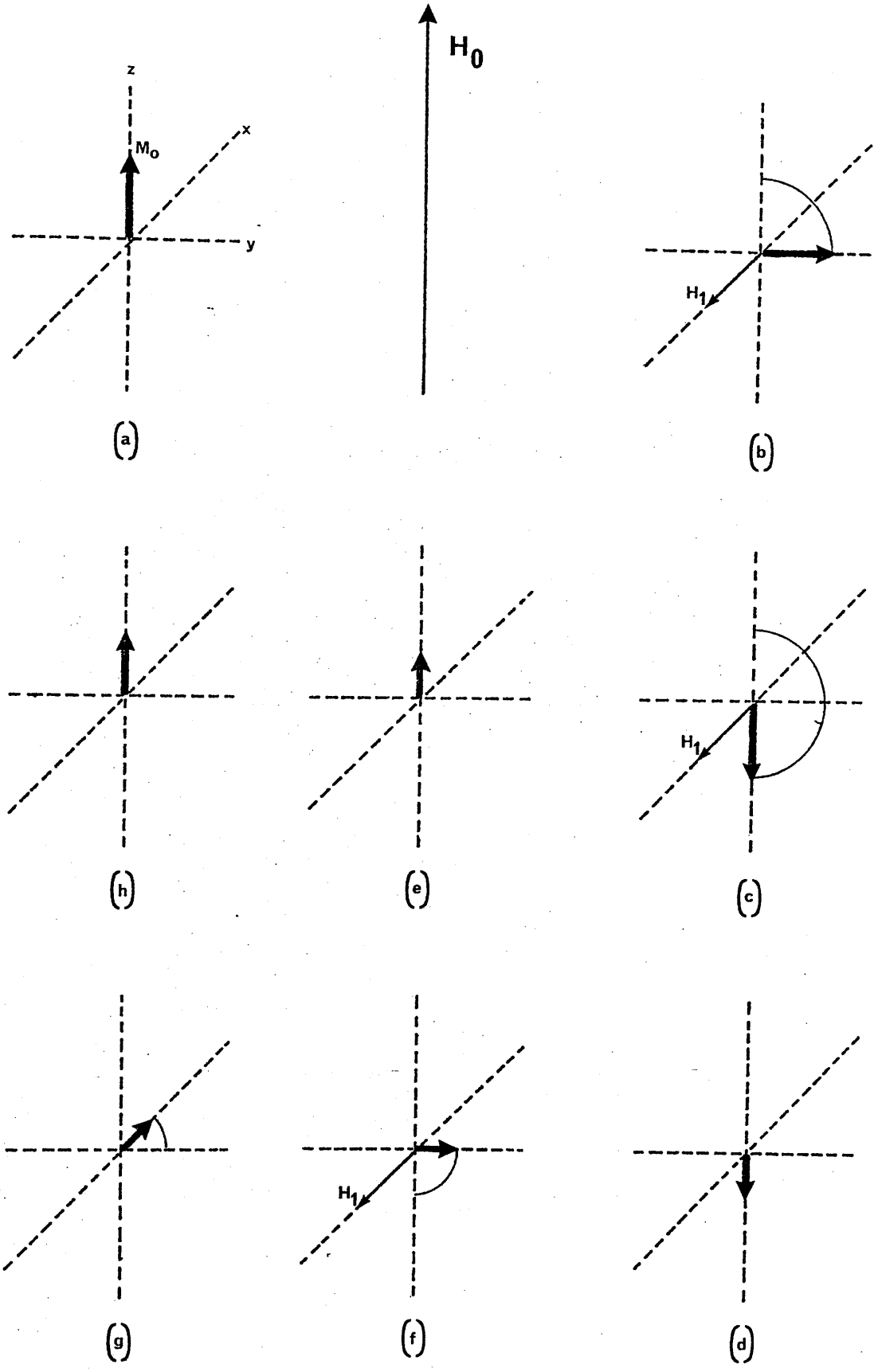


Figure 6.

THE THEORY OF THE CHEMICAL SHIFT[1,9]

For a given nucleus A, the precise resonance condition in an applied magnetic field H_o is given by :-

$$H_A = H_o (1 - \sigma_A)$$

where H_A is the magnetic field at resonance and σ_A is the screening or shielding constant which is a function of the chemical environment of the nucleus.

Attempts to calculate the value of this screening constant, the chemical shift, are based on the Ramsey equation[10] which was developed from second order perturbation theory. However, simplifications are generally employed such as the equation derived by Saika and Slichter[11] which partitions σ_A into several components :-

$$\sigma_A = \sigma_{dia}^{AA} + \sigma_{para}^{AA} + \sigma_{B\neq A}^{BA}$$

This was further expanded by Pople[12] who considered the third term as comprising of intra and interatomic electronic contributions :-

$$\sigma_A = \sigma_{dia}^{AA} + \sigma_{para}^{AA} + \sigma_{B\neq A}^{BA} + \sigma_{deloc}^{A} + \sigma_{solv}^{A}$$

In this equation, the first three terms are due to intra-atomic factors, the remainder to interatomic ones.

σdia^{AA}, the diamagnetic shielding factor is associated with the free movement of electrons round the nucleus in a spherically symmetrical state and its value may be calculated using the Lamb formula[13] :-

$$\sigma_{dia}^{AA} = \frac{e^2}{3mc^2} \quad \Sigma < r_i^{-1} >$$

where $< r_i^{-1} >$ is the mean inverse distance of the electron i from the nucleus and the summation is over all the electrons on the nucleus of interest.

σ_{dia}^{AA} is the major contributor to the overall σ_A value for protons because of their symmetrical electronic distribution but for nuclei with asymmetric electron clouds due to p or d electrons (e.g. ^{13}C, ^{19}F, ^{15}N) the dominant (90%) contribution[14] to the shielding factor is the paramagnetic term, σ_{para}^{AA}. It can be expressed as :-

$$\sigma_{para}^{AA} = \frac{-e^2h^2}{2m^2c^2} (\Delta E)^{-1} < \frac{1}{r^3} >_{2p} q_{AA} + \Sigma_{B \neq A} q_{AB}$$

where r is the distance between the nucleus and the 2p electrons in the case of ^{13}C nuclei, ΔE is the mean excitation energy, $\frac{-e^2h^2}{2m^2c^2}$ is a constant, the negative sign corresponding to the paramagnetic effect.

Obviously, a shortening of the distance between the 2p electrons and the nucleus will result in an increase in the negative value of σ_{para} and this is observed with electron withdrawing groups. A similar paramagnetic shift is expected if ΔE is decreased.

$\sigma_{B \neq A}^{BA}$ in the Pople equation is a summation of contributions to the shielding of A from intra-atomic currents induced in all atoms $B \neq A$ and is associated with their magnetic anisotropy.

The fourth term σ_{deloc}^{A} is an inter-atomic contribution associated with cyclic systems. It arises from nuclear shielding by ring currents produced by delocalised electrons. The term vanishes for acyclic molecules.

σ_{solv}^{A} is the contribution to shielding of A made by the solvent.

Calculations of σ_A afford results in reasonably good agreement with experimentally derived screening constants. It is found in practice that ^{13}C chemical shifts are largely additive under the effect of substituents and anomolies that do exist are due to direct substitution of electronegative group or heavy atoms, such as iodine.[15,16] Further shift effects occur due to carbon hybridisation and steric hindrance; sp^3 carbons occur at high field, sp^2 at low field and sp carbons intermediate; carbons that are sterically perturbed resonate at higher field than non-crowded carbons.

PARAMETERS REPRESENTATIVE OF THE ELECTRONIC PROPERTIES OF SUBSTITUENTS AND THEIR RELATIONSHIP WITH ^{13}C CHEMICAL SHIFTS

The dramatic effect a series of substituents can have upon ^{13}C chemical shifts (substituent chemical shifts, S.C.S.) is not always clearly understood. In an effort to simplify the situation, chemical shifts are considered in terms of parameters representative of substituent electronic properties. There are three main methods of estimating these electronic properties. They are :-

1) Group Electronegativity.
2) Hammett Constants.
3) Molecular Orbital (M.O.) Calculations.

GROUP ELECTRONEGATIVITY E_n [17]

The ability of an atom to attract electrons to itself is termed its electronegativity and since being coined by Pauling[18] in 1932, this concept has been widely used, despite the lack of standard electronegativity values. A useful approximation considers a polyatomic group as a pseudo-atom with a related group electronegativity and this data aids in the understanding of substituent effects on the reactivity and physical properties of organic molecules.

With the rapid advance of ^1H N.M.R. in the 1950's, attempts were made to construct an electronegativity scale using proton N.M.R. chemical shifts[19] but there was often poor correlation with other E_n values derived from alternative sources. Allred and Rochow[20] reported that the relative proton chemical shifts of methyl halides in infinitely dilute carbon tetrachloride solution were linearly related to previously assigned halogen electronegativities but this relationship could not be extended to other methyl derivatives.

^{13}C investigations carried out by Spiesecke and Schneider[21] in the early 1960's on the dependence of $\delta C - X$ in methyl, ethyl and phenyl derivatives on the X electronegativity, showed a paramagnetic (downfield) shift and good correlation with E_n when corrections were made for magnetic anisotropy effects in X.

Further studies on ethyl derivatives[22] showed that direct participation of the number of lone pairs on the substituent created either a para or diamagnetic shift depending on whether the

electronegativity or the number of lone pairs of the substituent increases.

Zetta and Gatti's[23] recent survey has revealed similar correlations in aromatic compounds; in benzylic compounds of the type $C_6H_5CH_2X$, the chemical shift of the methylene carbon is linearly related to the electronegativity of substituent X. A further aromatic example of this behaviour is provided by the para carbon atom of <u>para</u> substituted bromobenzenes[24] and <u>meta</u> dihalogenated benzenes.[25]

Since the electronegativity correlation takes no account of resonance or delocalisation effects, it is inappropriate to consider ^{13}C chemical shifts in terms of only this electronic parameter; therefore a more refined treatment of substituent electronic properties, such as Hammett constants, are more commonly used.

<u>HAMMETT CONSTANTS</u>[26,27]

The Hammett equation is a linear free energy relationship arising from the fact that a given substituent has similar effects on reactivity in different systems. It was originally used for reactions on side-chains of benzene rings for which the substituents were <u>meta</u> or <u>para</u> and took the form :-[28,29]

$$\text{Log } k = \log k^{o} + \rho\sigma$$

where k is the rate constant,

k^{o} is the rate constant for the unsubstituted compound,

σ is characteristic of the substituent and independent of the reaction,

ρ is determined by the nature and conditions of the reaction.

This led to σ constants, denoted as σ_M and σ_P for meta and para derivatives, respectively. Their values were calculated by arbitrarily assigning the value of ρ for the dissociation of benzoic acids in water at 25^o as one and σ of hydrogen as zero.

A major difficulty which arises when considering Hammett constants is their solvent dependence; most available experimental data is derived from aqueous or aqueous-alcoholic solutions where contributions from substituent-solvent interactions may be large (especially for hydrogen-bonding substituents such as -OH, NH_2) and difficult to remove. Until more gas-phase data are available, this problem must be endured. In an effort to refine and correct σ values Jaffe[29] reviewed more than two hundred reaction series.

The σ constant can only express the influence of a substituent on the rest of the molecule, and not its intrinsic properties. As primary steric effects are excluded, by virtue of the geometry of the aromatic system, electronic effects are most important. These effects can be understood in terms of combinations of inductive (I) and resonance (R) or mesomeric (M) effects. The I effect includes contributions from field effects and polarisation of σ and π bonds and operates from both meta and para positions and is principally descriptive of the effect of the substituent on its ring carbon atom. The M effect includes all effects which differ when a substituent is in the meta or para position, but mainly conjugation.

An over-simplification assumes that σp is the combination of I and M effects while σm contains only the I effect and therefore their difference (σ p - σ m) was taken as a measure of the M effect.[30]

However, this approximation neglects the possibility of direct mesomeric interaction between the substituent and the reaction centre. To overcome this problem, I effects were calculated by employing rigid cyclic systems where no direct conjugation could take place. Such σ_I values have been determined from the dissociation constants of 4-substituted bicyclo [2.2.2] octane - 1 - carboxylic acids in 50% (v/v) ethanol at 25°C.[31] A still better model is represented by dissociation constants of 4-substituted quinuclidines in water at 25°C.[32] but due to the poor availability of these compounds, the more common, but less precise α substituted toluic acids[30] are often used. A very simple and useful model defines σ_I from the pK_a's of substituted acetic acids,[33] assuming steric effects and intramolecular hydrogen bonding to be small. Many σ_I values have been determined from ^{19}F chemical shifts of 3-substituted fluorobenzenes[34] which has the advantage of high experimental precision, but results obtained deviate markedly from previous methods.

Due to similarities in the systems, Taft[35] proposed that σ_I values from bicyclo [2.2.2.] octanes were on the same scale as σ_M and σ_P values derived from benzene derivatives and consequently calculated mesomeric constants σ_R, from the equation :-

$$\sigma_R = \sigma_P - \sigma_I$$

From the scale of values obtained for σ_R, σ_M can be expressed as :-

$$\sigma_M = \sigma_I + \alpha\sigma_R$$

where α was found experimentally to be 0.33.

However, in the above equations, it was assumed that the inductive effect is the same from both meta and para positions. However, it is more strongly felt at the para position and therefore the general expression for the σ constant is given by :-

$$\sigma = \lambda\sigma_I + \alpha\sigma_R$$

where for σ_P, $\lambda = 1.14$, $\alpha = 1$

for σ_M, $\lambda = 1$, $\alpha = 0.33$

Values calculated for σ_R tend to be small, particularly when mesomerically electron withdrawing substituents are attached. Since σ_M and σ_P values derived from benzoic acids overestimate the mesomeric effects of donor groups compared to acceptor groups a new set of values was introduced, σ^o_{MP} [35,36] the unbiased values. σ^o values are obtained from the dissociation of phenylacetic acids where the interposed methylene group prevents direct conjugation between the substituent and the reaction centre. However, little improvement is gained by substituting σ^o_P values for those of σ_P when calculating σ_R.

It has been proposed,[37] that the mesomeric constant, σ_R, has no universal scale but instead four different scales must be employed to define this contribution in various situations :-

1) σ^o_R for weak π donors such as halogens,
2) $\sigma_{R(BA)}$ for weak to moderate π acceptor groups such as benzoic acids,
3) σ^+_R for systems with a net positive charge,
4) σ^-_R for systems with a net negative charge.

The use of single reactivity parameters, σ_p or σ_M, in correlating substituent effects is limited, since each parameter is a mixture of an I and M effect and linear relationships with substituents are obtained only when the I/M ratio is the same in the observed effect and the reactivity parameter. Swain and Lupton[38,39] strongly criticized the proliferation of scales of polar substituent constants and attempted to simplify the situation by attributing to each substituent just two basic electronic characteristics: a field constant, F which includes the field (direct) effect and the inductive (through bond) effect and a resonance constant R. This method proposes that the numerous sigma scales are not independent but each is a linear combination of F and R as in the equation below :-

$$\Delta = fF + rR$$

Δ is the experimental substituent effect,

where f and r are weighting factors of F and R.

To obtain the resonance scale, it is assumed that the substituent $\overset{+}{N}Me_3$ is incapable of participating in a mesomeric interaction and thus has a value of 0 on the R scale; hence the value of R for other substituents can be calculated from the equation :-

$$\sigma_p = \alpha F + R$$

where $\alpha = 0.56$ (from R = 0 for $\overset{+}{N}Me_3$).

The percentage resonance effect is given by :-

$$\% R = \frac{100\ \psi\,|r|}{\phi\,|f| + \psi|r|}$$

where $\phi = 0.365$ and $\psi = 0.228$.

ϕ and ψ are scale factors to correct for the different numerical ranges of F and R scales.

A second Dual Substituent Parameter (D.S.P.) approach by Taft[37] which involves combinations of σ_I and the appropriate σ_R value described previously results in an equation of the form :-

$$\Delta = \rho_I \sigma_I + \rho_R \sigma_R$$

where Δ is again the experimental substituent effect and ρ_I and ρ_R are the weightings of σ_I and σ_R respectively.

Several workers in the field of N.M.R. spectroscopy have been attracted to multi-parameter treatment of the Hammett Equation. Reynolds[40] has used the Swain - Lupton method in correlation analysis of chemical shifts and coupling constants of ^1H or ^{13}C of various systems including para-substituted styrenes. Wiley and Miller[41] applied D.S.P. techniques to the proton N.M.R. of N-trimethyl-phenylammonium iodides $X\text{-}C_6H_4\text{-}\overset{+}{N}Me_3\ I^-$ but their results put in doubt the applicability of the method. Phillips et al[42] used the following equation in their study of substituent effects on ^{19}F chemical shifts in aromatic systems :-

$$\Delta = f'F + r' \sigma_P$$

where f' and r' are weighting factors.

In this formalism, F represents effects transmitted through space and through the σ bonded framework whereas σ_P is claimed to measure those effects transmitted through the π system. The evidence for this is that the substituent effects on the ^{19}F chemical shifts of 4-X, 4'-F substituted trans-stilbenes correlates with σ_P and since eleven bonds separate the fluorine atom from the substituent, inductive effects should be negligible; the substituent

effects should be completely transmitted via the π system, hence σ_P is the best measure of effects transmitted in this manner.

The use of the Dual Substituent Parameter approach to rationalise substituent effects has been the subject of much controversy. A strongly disputed area has been that of the R values employed in the Swain - Lupton method;[38,39] several authors[43,44,45] have pointed out that the said values depend critically on the assumption that NMe_3^+ has no resonance effect, but this group is isoelectronic with ^tBu which is known to exert a resonance contribution and there seems to be no reason for excluding this possibility for NMe_3^+. Further criticism of this approach comes from Exner[26] who disputes the use of a general resonance scale for all situations and points out that the standard deviations obtained in correlations between the σ_P^+ and σ_P^- scale and F and R are too large.

Taft's D.S.P. treatment has also had criticism levelled at it due to its use of seven variables σ_I, ρ_I, ρ_R and four σ_R values. Phillips[46] notes that employing this number of degrees of freedom would allow any substituent effect to be correlated and further, that spurious mechanisms of electronic effects could be arrived at by this method.

Phillips' assumption[42] that changes in ^{19}F chemical shifts for the stilbene series are completely due to resonance interactions was disputed and subsequently modified. However, Taft[47] claimed that the correlation observed was purely fortuitous and would not be valid in a different solvent, on the basis that solvent effects cause a variation in the σ_R : σ_I ratio for similar systems with different

groups linking the phenyl rings (e.g. azobenzenes, diphenyl methanes).

In support of D.S.P. methods and, in particular, Taft's scheme, is a recent study carried out by Mezey and Reynolds, who constructed multiparameter scales for 4-substituted styrenes[48] and 4-substituted benzoic acids[49] based on ab initio molecular orbital calculations for these systems. The results which they obtain convinces them of the validity of Swain and Lupton's earlier work regarding a substituent electronic properties of separate field and resonance effects. Secondly, they agree with Taft's argument that while there is a common field scale, there is no such universal resonance scale.

Several other multiparameter extensions of the original Hammett equation have been made and, in particular, that of Yukawa and Tsuno[50,51] which takes account of situations where direct mesomeric interaction is possible, is worthy of note. Deviations are commonly shown by para-substituents which possess considerable mesomeric or resonance effect. Anomalies were apparent to Hammett himself in his work on the correlation of reactions of anilines and phenols. These deviations of the p-NO_2 substituent were systematic in that a σ value of ca 1.27 seemed to apply, compared with 0.78 based on the ionization of p-nitrobenzoic acid. This apparent irregularity is explained by cross-conjugation, i.e. conjugation involving substituent and reaction centre. Yukawa and Tsuno proposed a method for dealing with a system which has a net positive charge, i.e. reactions that are more electron-demanding than the ionisation of benzoic acid and have substituents with powerful resonance effects. They modified the Hammett equation to incorporate enhanced resonance

effects as shown :-

$$\text{Log } k = \log k^{o} + \rho (\sigma + r \Delta\sigma^{+})$$

where $\Delta\sigma^{+} = (\sigma^{+} - \sigma)$ i.e. $\Delta\sigma^{+}$ is the enhanced value of σ and r is a constant, similar to, but independent of, ρ .

A corresponding equation formulated by Yoshioka et al[52] deals with the influence of -K substituents (e.g. NO_2, CN, CO_2H) on reactions that are less electron demanding than the ionisation of benzoic acid, i.e. have a net negative charge :-

$$\text{Log } k = \log k^{o} + \rho (\sigma + r\Delta\sigma^{-})$$

where $\Delta\sigma^{-} = (\sigma^{-} - \sigma)$.

Values of σ^{-} have been used in the correlation of data for the reactions of aniline and phenol derivatives, of carbanions, and nucleophilic aromatic substitution. Values of σ^{+} have been applied to solvolyses, aldehyde reactions, basicities of carbonyl compounds and amides, radical reactions and electrophilic aromatic substitution.

MOLECULAR ORBITAL CALCULATIONS[53,54,55]

Molecular orbital methods have been developed to the stage where they can aid in the calculation of some observable properties of organic compounds, resulting in a fair degree of accuracy.

Although a basic self-consistent field (S.C.F.) approach is used in all these valence electron semi-empirical molecular orbital methods, evaluation of the large number of integrals which cannot be quantitatively calculated, varies with different orbital methods. The S.C.F. technique requires the calculation of the total energy of the system by an iterative method involving approximate expressions

for the relevant wave functions and Hamiltonian operators, until the total energy converges to a minimum on successive interation. This procedure generates a density matrix from which bond orders and charge densities may be extracted.

In a priori M.O. methods all the integrals are evaluated rigorously by substitution of complex functions for each atomic orbital in the total wave function. This process is impractical for molecules of more than two atoms. Therefore, in order to conduct the calculations on complex molecules certain approximations have to be made to reduce the computation: these simplifications involve various degrees of neglect of differential overlap which is the product of the wave functions of the two atomic orbitals.

In the Complete Neglect of Differential Overlap (C.N.D.O.) method, the differential overlap between any pair of orbitals on the same centre is taken to be zero.[55] The Hamiltonian operators are estimated by parameterisation, i.e. by substituting experimental data into an expression for the Hamiltonian. In the CNDO/2[55] method, the average of the Ionisation Potentials and Electron Affinities are used to approximate the Hamiltonian of an atom. The wave functions are constructed from Slater - Type Orbitals (S.T.O.) and these functions are used in the iterative processes previously described. This method has found application in bond angle and length calculation as well as predicting N.M.R. chemical shift trends.

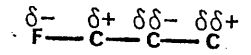
A slightly more advanced approach is that of the Intermediate Neglect of Differential Overlap (I.N.D.O.) method which takes account of differential overlap between orbitals on the atom.[56,57] A

further variation is that it allows for the electrons having parallel or anti-parallel spins and hence this procedure can be used to calculate spin densities and hyperfine coupling constants.

The Partial Neglect of Differential Overlap (P.N.D.O.)[58] and the Modified Intermediate Neglect of Differential Overlap (M.I.N.D.O.)[59,60] methods are basically variations of the I.N.D.O. procedure and have been used to calculate several molecular parameters.

The highest level of semi-empirical theory is ab initio[61] theory where 1s electrons are included as part of an unpolarisable core. In this method, gaussian orbitals are used which allow more rapid evaluation of the two electron integrals which are neglected or parameterised in the previous methods.

Although the ab initio method is acknowledged to be the most accurate, it is time-consuming to operate and, for this reason, C.N.D.O./2 calculations are more widely used, despite their inherent weaknesses, especially in generating unreliable energy values for various properties. There have been many examples where the results of molecular orbital studies have not been in accord with predictions of popular theories. A C.N.D.O./2 calculation[56] on simple molecules revealed a charge density distribution which could not be accounted for by the nature of the inductive effect as it was then understood. The M.O. study predicted that the polarisation of a saturated hydrocarbon induced by substituents produced charge redistributions which did not fall off monotonically with increasing distance from the substituent, but instead alternated as shown in 1.



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However, in using molecular orbital methods, care must be taken in interpreting the results obtained. Fliszar et al[62,63] point out that electron distributions within molecules are normally determined by using the Mulliken population analysis, in which the overlap population associated with a pair of bonded atoms is arbitrarily divided equally between the two, but in practise the real electronic charge distribution between two dissimilar atoms may be very different from that calculated.

THE ^{13}C CHEMICAL SHIFTS OF ORGANIC COMPOUNDS

ACYCLIC SYSTEMS

Grant and Paul[64] published a comprehensive study of ^{13}C spectra of linear and branched alkanes in 1964 in which they examined saturated hydrocarbons containing up to ten carbons. Results show that the "methane" carbon experiences a progressive downfield shift on successive substitution by methyl groups and that this trend is universal. Similar substitution of a β hydrogen also leads to deshielding. However, methyl substitution of the γ hydrogens causes a shielding effect, the so-called γ effect which is thought to arise from a "through space" interaction rather than a "through bonds" mechanism.

The consistent shift trends that were obtained from this study enabled Grant and Paul to employ an incremental system to predict the chemical shifts in linear alkanes to an accuracy of 0.21 ppm. In order to predict shifts for branched systems, additional parameters are required.

In an alternative approach, Savitsky and Namikawa[65] investigated the possibility of an additive relationship for predicting chemical shifts using carbon shieldings and by employing a least squares analysis, a series of bond parameters for structural modifications was calculated. The inclusion of an additional factor for the γ effect enables shieldings to be predicted to within 2 ppm.

Lauterbur[66] initiated a systematic study of substituted alkanes, halomethanes $CH_{4-n}X_n$ where X = Cl, Br, I and observed that ^{13}C shieldings followed a regular trend, with greatest shielding when X = I.

Another observation of the study was that additive shift changes were produced by the interchange of halogens in polyhalogenomethanes. Litchmann and Grant[15] attempted a theoretical analysis of the halomethane results and concluded that halogen substitution caused steric perturbations of the effective orbital nuclei which in turn has the effect of elongating the carbon - halogen bond.

Further alkyl halide studies[67,68] show constant substituent effects in systems of three or more carbons. The α chemical shift effects roughly correlate with halogen electronegativities, while the β effects are similar for each halogen. γ effects are shielding, the effect decreasing with increasing size of halogen.

Roberts et al[69] have examined a series of acyclic alcohols in order to determine the influence of the hydroxyl group on alkyl carbon shieldings. Their findings show that the alcohol moiety causes a definite downfield shift (deshielded) on the α carbon with attendant smaller deshielding of the β carbon. In an analogous manner to the halogens, an upfield (shielded) γ shift occurs. However, the substituent effect of the hydroxyl function depends upon its location along the alkyl chain and furthermore chain branching may diminish the effect possibly due to small variations in the polarisability of the alcohol group.

Similar trends have been noted for carboxylic acids and their anions,[70] namely deshielding α and β effects and shielding γ effects. The α effect is enhanced in the carboxylate anion case which is surprising, since it depends on the electron withdrawing power of the substituent which in this situation is greatest for the free acid. Hagen and Roberts have found that the rate of attenuation

of the substituent effect in the acid and the anion along an alkyl chain is close to that expected for a $< r^{-3} >$ dependence in the situation where the negative charge is centred between the oxygens of the carboxyl group and the alkyl chain is in the extended staggered conformation. This result mirrors previous work on aliphatic acids and anions which dealt with proton shieldings;[71] it has been rationalised in terms of a "through space" substituent effect. However, other workers are more inclined towards the alternative explanation[72] of C - H bond polarisation caused by the negatively charged carboxylate anion.

As expected, nitroalkanes[21,66] show the largest deshielding α effect, but the associated β effect is small and progressively decreases with increasing α methyl substitution.

ALICYCLIC SYSTEMS

Carbon resonances of the simplest cyclic system, cyclopropanes, are found at higher fields than expected for such compounds.[73,74,75] This anomalous behaviour was accounted for by assuming the presence of a ring current corresponding to 3.5 electrons in a radius of $1.10^{o}A$.[76]

Various studies[73,74,75] have been carried out on substituted cyclopropyl rings. It is found that polar substituents deshield the α carbon, with the exception of iodine and cyano which have a large and small shielding effect respectively. Excluding these examples, the α effects are similar to those in monosubstituted methanes reported previously.

A comprehensive investigation by Lippmaa et al[77] of thirty six monosubstituted cyclohexanes revealed interesting and somewhat surprising relationships. It was found that linear correlations existed between the α and β carbon chemical shifts of the rings and the corresponding carbon shifts of similarly substituted isopropyl groups. Since the chemical shift observed for the cyclohexane ring is the statistical mean of the axial and equatorial conformers and their distribution at equilibrium is dependent upon the substituent then such a correlation is unusual. Low temperature N.M.R. has enabled investigations of substituent effects for single conformers of cyclohexyl derivatives.[78,79] A linear correlation exists between the γ carbon shieldings and the electronegativity of the substituent, especially when the substituent is a halogen and in the equatorial position. Axial substituents produce larger γ shieldings but the shielding does not increase with the effective size of the substituent.

The long range δ effect in cyclohexanes[77] is shielding, whereas in comparable acyclic derivatives (e.g. n - pentanes) the δ carbon shows little variation with change of substituent. This is taken as evidence of different mechanisms of transmission operating for the two systems. Since equatorial substituents, which have a small steric effect on the δ carbon, produce the greatest δ effects, it is assumed that the δ effect is transmitted by a "through bond" mechanism. This rationale is substantiated by reasonable correlation between the δ - chemical shifts and the inductive parameter σ^*.

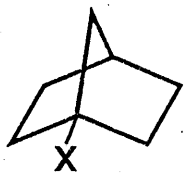
POLYCYCLIC SYSTEMS

In polycyclic systems, additivity parameters, which are employed so successfully in acyclic systems to predict carbon shieldings are of limited value.

Grutzner and Roberts,[80] studying the chemical shifts of a series of 2-substituted norbornanes, showed that the substituents produce effects similar to those in acyclic systems but with important differences. The orientation of the substituent (exo or endo) has little effect on the α and β parameters, but has a major effect on the magnitude of the γ effect. The endo - 2α and β effects are slightly smaller than those in the exo - 2 case (by 1 - 2 ppm) which may be due to the introduction of additional steric interactions in the endo case, causing distortion of the ring system. The three γ positions, C(4), C(6) and C(7) experience different effects from the substituent at C(2) and in addition the γ effect is altered by the orientation of the substituent. Small effects are encountered for C(4) and due to its remoteness from the perturbing site, a steric interaction can be eliminated. However, steric perturbation may have an effect on C(6) when the substituent is endo and on C(7) when the substituent is exo. Both substituent orientations cause a shielding of C(6), the greater for exo. The endo shielding correlates approximately with the size of the substituent and this has been cited as evidence of a steric interaction; the exo shielding, on the other hand, correlates with substituent electronegativity. This observation has been rationalised in terms

of a mechanism which considers a possible overlap of the back lobes of C(2) and C(6) orbitals in a similar manner to "W" long range proton - proton coupling $^{4}J_{H-H}$.[81] The γ effect at C(7) is deshielding for endo and shielding for exo and neither of these shifts can be related to electronegativity parameters.

Several studies have been made on bridgehead substituted polycyclic compounds (norbornanes 2,[82] adamantanes 3,[83] and bicyclo (2.2.2) octanes 4[84,85]) and the results obtained are in agreement that the shift effects follow the trend $\alpha > \beta > \gamma > \delta$



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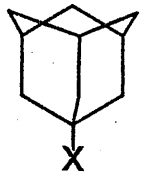

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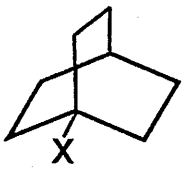

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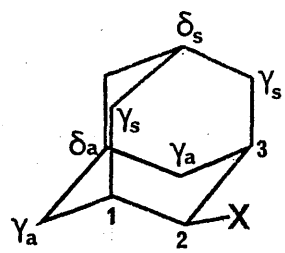
However, although the C(1) α shifts of 1 - adamantyl and bicyclo (2.2.2) octyl systems correlate well with each other, there is no good relationship with those of the 1 - norbornanes. The large degree of strain at C(1) of the norbornanes compared to the identical positions on the other two systems is probably responsible for the lack of uniformity in the α shifts. β shieldings in all three systems correlate well and appear to operate via a "through-bond" mechanism. Similar results are found for the γ - substituent effects.

Investigations on the more strained nortricyclene and quadricyclane systems reveal some interesting effects.[80] As expected, the cyclopropyl carbons resonate at high field, but due to the ring current effect associated with the cyclopropane ring, the remaining carbons in the system are shifted upfield compared to norbornane.

A study on 1 - substituted adamantanes[83] disclosed the dependence of α and β effects on steric and inductive factors. The substituents were divided into two groups according to their effects on the β carbon. Class 1 substituents contain no more than one atom heavier than hydrogen and within this group the more electronegative substituents give smaller paramagnetic shifts. Class II substituents contain two or more atoms heavier than hydrogen and they produce smaller β effects than those of Class I. In a series of 4 - substituted tricyclenes[85] an analogous division of substituents into two classes can be made. γ effects, which were accounted for in 1 - adamantanes by steric considerations, may be due to hybridisation differences of the γ carbons in the two series, since skeletal deformation is unlikely for the more rigid tricyclenes.

Due to the electron-withdrawing nature of the exocyclic double bond in 1 - substituted camphenes,[86] the substituent bearing carbon, C(1), absorbs at lower field than in other bridgehead substituted systems. Nevertheless, an acceptable correlation is still found between the α shift and E_n, the electronegativity of the substituent; a similar correlation is found to exist between the β effects of the olefinic C(2) carbon and the linear free energy parameter σ_I.

A number of investigations have been carried out on non-bridgehead substituted systems; in one such survey a series of 2 - substituted adamantanes[83] was employed, 5 and 6.



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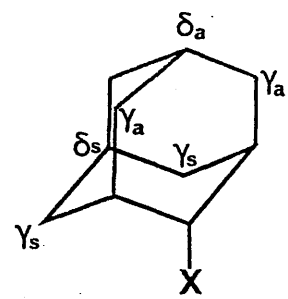

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There is a strong interaction between the substituent and the γ syn carbons in this series, resulting in shifts to higher field of these carbons; γ anti carbons experience little effect. The long range δ effect is equal for both syn and anti carbons, with more electronegative substituents producing larger high field shifts. This effect is attributed to a "through the bond" mechanism since the δ carbons are supposedly too distant for "through space" interactions. Duddeck[87] has questioned the assumption that no steric interaction occurs between X and the δ carbons.

Chemical shift assignments in non-bridgehead substituted systems have at time been based on the premise that steric crowding results in upfield shifts, an assumption that is now being disputed.[88,89]. It has recently been reported that sterically unperturbed δ carbon atoms in both norbornane and adamantane systems are more shielded relative to other more sterically perturbed δ carbon atoms also

present in the molecule. Further evidence contradicting the rule of steric compression was reported by Giannini,[90] who, working on halogen substituted cortisols noted the largest upfield shifts for γ carbons were produced by fluorine.

Eliel et al[91] undertook an extensive study of the γ effect and the dependence on conformation for systems with well-defined stereochemistry. Results indicate that greater shielding effects are found for carbons anti to a substituent containing first-row elements or a heteroatom than for those gauche to that substituent or heteroatom. Mechanisms involving "through the bonds" or "through space" effects to account for the observed shifts are not applicable as there is no correlation with E_n or σ_I. Eliel's group suggested a hyperconjugative interaction between the free electron pairs on N, O and F atoms and the $C_\alpha - C_\beta$ bond, with an attendant alternation of the electron density at the γ anti-periplanar carbon as shown in figure 7.

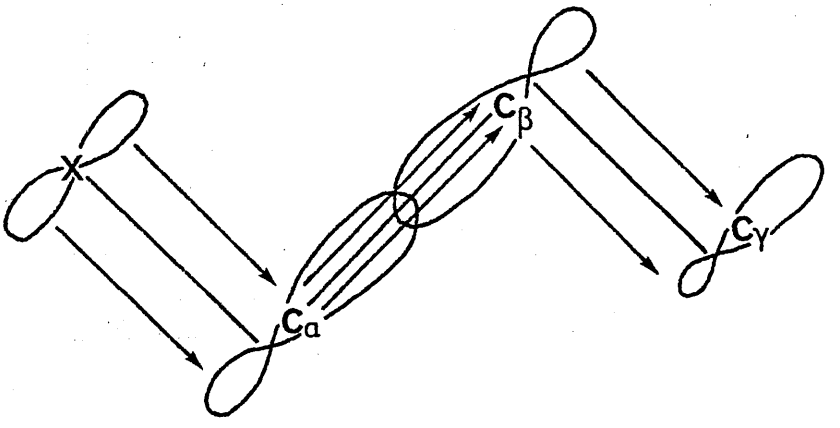
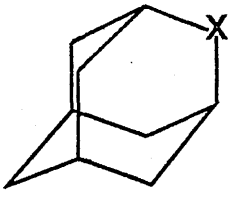


Figure 7.

The shorter length of the C - X bond in these cases and the similar radial dimensions of N, O, F and C favour partial π bond involvement and hence this mechanism for first-row atoms. An exception to this rule for γ anti carbons occurs when the heteroatom is attached to the bridgehead carbon. Duddeck[92] discovered that the γ effects produced by the heteroatom in 2 - heteroadamantanes 7 where the said atom is attached to two bridgehead carbons, are not significantly different from γ syn effects in 2 - substituted adamantanes where the substituent bearing carbon is not at the bridgehead. This is evidence that the exception to the rule reported by Eliel[91] is restricted to γ anti effects and is not valid for γ syn effects.

Eliel's proposal of a hyperconjugative mechanism to account for the γ effect is not universally accepted. A back-lobe interaction mechanism is preferred to explain γ - anti-effects in 7 - substituted norcaranes 8 where the γ anti-shielding effect of a methoxy group is identical to that of chlorine and bromine and a rough correlation is found between the γ -anti effect and substituent electronegativity.[93] Several other explanations of the γ effect have been suggested, including the dependence upon bond angle changes[94] which would explain the upfield γ gauche effect in ^{31}P and ^{19}F N.M.R. studies.



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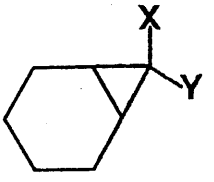


8

AROMATIC SYSTEMS

Many ^{13}C studies of aromatic systems[66,95] have been made and among the pioneers of this work were Spiesecke and Schneider.[95] These workers found that the chemical shift of the substituent bearing ring carbon in monosubstituted benzenes correlated with substituent electronegativity, if account is taken of substituent anisotropy.

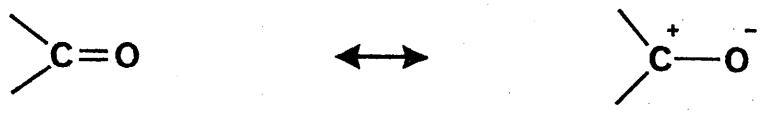
Ortho carbon resonances cannot be interpreted by any known parameter such as E_n or σ values. Many factors such as anisotropy, inductive and resonance effects operate on this position and their contributions will vary with different substituents.

Chemical shifts associated with the meta position have a small range (< 5 ppm) for a wide variety of substituents (c.f. 96.7 - 163.3 ppm for the ipso carbon) and this is taken as part of the evidence that the π inductive effect controls ground state electron density. Consequently, this effect determines the meta carbon chemical shift in monosubstituted benzenes.[96]

The most important factor affecting chemical shifts of the para carbon will be changes in π electron density brought about by the resonance effect of the substituent. Good correlations of the para carbon chemical shifts with the Hammett σ_p constants are found.

CARBONYL SYSTEMS

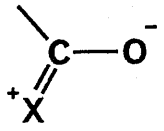
^{13}C signals for carbonyl carbons are generally found appreciably downfield of other common functional groups. This deshielding effect is mainly due to polarisation of the carbonyl π bond towards oxygen as in fig.8, where contributions from b are important in the overall electronic distribution.



a b

Figure 8

In amides and esters, the electronegative group α to the carbonyl, can conjugate with the π system as shown in 9, resulting in higher electron density at the carbon with an attendant upfield shift in the ^{13}C spectrum.



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Aldehydes and ketones resonate at lower field compared to the unsubstituted carbonyl group, formaldehyde. Savitsky, in a study on compounds of the type CH_3-CO-X showed that although the above

trend is qualitatively correct, the ^{13}C chemical shifts of the carbonyl carbon do not follow a recognisable inductive order.[97]

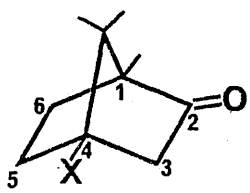
By comparing chemical shifts of alkyl cyclohexanones with alkyl cyclohexanes, the effect of a carbonyl group on the shieldings of a cyclic system was examined. Weigert and Roberts[98] found that, as expected, α carbons were considerably deshielded but γ carbons were shielded.

Several studies[97,99] undertaken on cyclic as well as acyclic systems suggest that an important factor contributing to the carbonyl shieldings is the mean excitation term ΔE, which appears in Pople's expression for the paramagnetic shielding constant. The $n \rightarrow \pi^*$ transitions associated with ΔE are found to correlate reasonably with the carbonyl carbon chemical shifts in several systems and this tends to indicate that the effect of electron density on $\langle r^{-3} \rangle_{2p}$ is a minor factor in these examples.

The ^{17}O shifts of the carbonyl oxygen have also been studied, and reveal the same general trend as with the carbon resonances.[100] However, some anomolies exist[101] where shifts are moved to lower field by high excitation energies and this behaviour has been rationalised in terms of increasing polarisation of the carbonyl group. ^{17}O chemical shifts of substituted acetophenones[102] do not correlate with $n \rightarrow \pi^*$ transitions possibly due to the fact that this transition is not a good approximation to ΔE in aromatic systems as $\pi \rightarrow \pi^*$ transitions occur at similar energies.

A study on several substituted cyclohexanones[103] was carried out and reveals that substituent shifts derived for methyl substitution at the carbon adjacent to a carbonyl show a dependence upon the dihedral angle between the two groups.

The substituent chemical shift (S.C.S.) concept has been widely used to investigate the effect of structural changes in a molecule, on the ^{13}C chemical shift of the carbonyl carbon. In 4 - substituted camphors 10[104]



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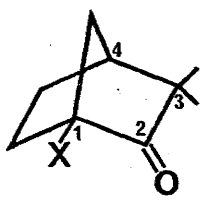

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electron-withdrawing substituents shield the carbonyl carbon and show a reasonable correlation with σ_I. The α and β effects in this system mirror those of the saturated 4 - substituted tricyclenes.[85] By placing the carbonyl, β , to the bridgehead position in a rigid system, as in 1 - substituted camphenilones 11,[105] greater shielding occurs with electron-withdrawing groups and as before a correlation with σ_I exists which on account of through space interactions of the substituent and carbonyl group is not as good as found with 4 - substituted camphors.

PART 2

PYROLYSIS OF ACETATES

As early as 1854,[106] it was known that if a β-hydrogen was present in the alkyl portion of an ester, $RCOOCR'_2CHR''_2$ then decomposition into the corresponding acid (RCOOH) and olefin ($R'_2C = CR''_2$) was feasible at elevated temperatures (300 - 550°C).[107,108] Hurd and Blunk[109] later proposed a cyclic hydrogen bridge mechanism for the pyrolysis, (fig.9) based on the fact that, generally, only two products were formed and at low temperatures. The chelate type

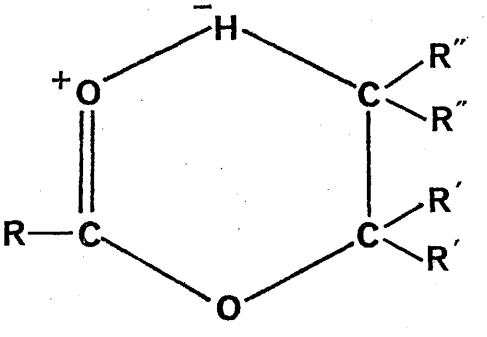


Figure 9.

of six-atom ring closure via a hydrogen bridge, envisaged by these workers was the earliest description of what is now known as the cyclic concerted transition state, which accounts for the unimolecular nature of the reaction. Other mechanisms were suggested to account for the observed reaction and its kinetics; in particular, radical chain decomposition which was assumed to be important in the pyrolysis of esters lacking β-hydrogens.[110].

Stereochemically, a cyclic, concerted process as put forward by Hurd and Blunk necessitates a syn or cis elimination, a fact which has been demonstrated by a number of studies.[111,112] In the simplest of these, it was shown that elimination did not take place in the absence of cis - β hydrogen atoms, or at least was so much slower as to imply an alternative mechanism.

Several studies have been undertaken to verify the cyclic concerted process and results obtained can be divided into two classes :-

1) Data referring to C - O bond breaking;
2) Data referring to C - H bond rupture.

1) Rate differences recorded for various esters (tertiary, secondary and primary) were too small for much carbonium ion character in the pyrolysis.[113] One of the most striking confirmations of the relatively small importance of carbonium ion stability was found in kinetic studies by Depuy et al,[114] who employed a series of esters, standardised by 5 - nonyl acetate.

Several workers studied the effect of acid strength on ease of pyrolysis,[115] and their work revealed that esters of stronger acids underwent elimination more easily than esters of weaker acids and that there existed a correlation between acid strength and pyrolysis temperature (rate of reaction).[116]

2) The most direct measure of the importance of the carbon - hydrogen bond breaking in the transition state can be obtained by the effect on the rate of replacing a hydrogen by deuterium. The kinetic

isotope effect was first observed in acetates by Curtin and Kellom in 1953[117] and since then many other investigations of ester systems have been carried out,[118, 119] all of which report quite large $k^H/_kD$ values which were interpreted in terms of a concerted process involving a six-membered cyclic activated complex where a large amount of $\beta C - H$ bond breaking had occurred. Although an isotope effect was found for all the systems studied, the magnitude of it varied considerably (1.7 - 2.8)[120] and in some cases was larger than the theoretical maximum at a given temperature.

Since 1960, renewed interest has centred round the mechanism of ester pyrolysis. The original proposal of a concerted mechanism with no separation of charge was abandoned in favour of a process with a certain amount of ionic character. Studies on 1 - arylethyl acetates[121] and 1,2- diarylethyl acetates[122] gave rate constants which correlated with σ^+ values in a Hammett plot and a negative rho value of -0.66. This showed conclusively that the α-carbon possessed appreciable carbonium ion character in the transition state. Other investigations of substituent effects confirmed the polar character of the reaction and hence disproved Hurd's mechanism[109] of a fully concerted process in which all the electrons moved simultaneously. Electron withdrawing substituents in the acid function[123, 124] and electron releasing groups in the α position of the alkyl moiety[125, 126] bring about an increase in the rate. The influence of β-substituents in the alkyl function is less well understood, but it appears that alkyl groups have a small accelerating effect, while electron withdrawing substituents such as Cl, OMe

have a small retarding influence.[126] However, Emovon and Maccoll[127] noted that an acetyl group substituted at the β - position gave a large rate increase.

Various mechanisms were put forward to account for the experimental facts, differing only in the amount of polarity or charge accumulation in the transition state. Maccoll and Emovon suggested that the ease of breaking of the alkyl - oxygen bond and the β - carbon - hydrogen bond in a heterolytic manner was of importance in accelerating the reaction and concluded that an ionic transition state may exist. In such a process, the C_α - O bond would be ruptured heterolytically forming an ion pair and although more energy would be required compared to a homolytic cleavage, this would be offset by the Coulombic interaction.[128,126] Objections to this mechanism[129, 114] were based on the fact that the known isotope effect could not be accommodated in such a scheme. However, Scheer et al[126] proposed that the formation of the ion pair was reversible as shown in figure 10, where A^*

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^* \xrightarrow{k_2} \text{Products}$$

Figure 10.

represents the ion pair; if k_{-1} was much larger than k_2 then a large isotope effect was feasible.

Mechanisms falling between the two extremes of fully concerted and ion pair processes were suggested by several workers.

Tinkelenberg et al[130] proposed a concerted heterolysis in which the alkyl - oxygen and β - carbon - hydrogen bonds were strongly polarised, while Smith et al[121] preferred a concerted process with some charge separation, resulting in the partial formation of a carbonium ion at C_α, both of which appear rather vague.

An ion-pair intermediate in rapid equilibrium with the ester, as Scheer suggested[126] would result in scrambling of the oxygens in the ester prior to thermolysis. However, partial thermolysis (40%) of ethyl acetate enriched in ^{18}O, $Et^{18}OCOMe$, carried out in a deactivated reactor revealed that only a minor amount of scrambling had taken place. Therefore, rapid equilibration does not occur between the ester of primary alcohols and an intimate ion pair during pyrolysis.[131]

Clearly then, experimental data obtained from various studies indicate a pyrolysis mechanism in which a certain degree of charge separation has occurred but no actual bond cleavage into a discrete ion pair has resulted. To what extent has bond-making and bond-breaking reached in the transition state? Smith and Taylor in a systematic study of 1-arylethyl acetates[121] and 1,2 - diarylethyl acetates[122] have provided evidence for detailed evaluation of the cyclic process. As noted earlier, rate constants for these compounds with substituents at the α - carbon, in this case substituted aromatic rings, correlate well with the Hammett σ^+ parameter resulting in a ρ value of -0.65. The rate constants for the same system with similar substituents now at the β - carbon yield a linear relationship with σ and a rho value

of + 0.08. This was taken to imply that the positive charge developed at the α - carbon was approximately four times larger than the corresponding carbanion character at the β - carbon. However, such a rationale contradicted the evidence of the kinetic isotope effect which had indicated the importance of the β - hydrogen cleavage in the transition state.[129] In an effort to clarify the situation, Taylor[120] repeated several kinetic studies undertaken previously, employing more rigorous experimental techniques (static kinetic method) and taking into account possible hyperconjugative effects, it was found that the pyrolysis of 1,2 - diphenylethyl acetate did indeed have a primary isotope effect the magnitude of which was calculated to be 2.14 as opposed to Curtin and Kellom's original evaluation of 2.8[117]. However, it is believed that the maximum isotope effect, in this study, 2.70, is achieved when the hydrogen is only half transferred.[132] This maximum applies when transfer occurs between atoms of like basicity but in this example the greater basicity of oxygen relative to carbon should mean that the maximum isotope effect will be obtained when the hydrogen is less than half transferred, and perhaps as little as one third. Since the observed isotope effect is less than 80% of the theoretical maximum, then it may be assumed that the β - carbon hydrogen bond is no more than one third broken in the rate determining step.[120]

The earlier assumption of Taylor relating to the extent of charge development has been modified to take into account the fact that substituents stabilising a positively or negatively charged ion will, to a certain extent, destabilise an oppositely charged species adjacent to it. Employing this approach, the charge at the

α - carbon is reduced to only 1.65 times larger than that at the β - carbon in the transition state.[120].

The effects of various substituents at the α and γ carbon atoms have been thoroughly examined and are well understood. Heterolytic character has been shown to increase along the series acetates < phenylacetates < benzoates < carbamates < carbonates[133] and along the series primary < secondary < tertiary.[134] However, β- carbon substituent effects have been studied less extensively and the results obtained show considerable disagreement with each other.[121, 122, 126, 127. The lack of uniformity in the β - substituent effects has been put down to several factors;[135] (a) the conflict of inductive and mesomeric effects; (b) the primary and secondary effect of substituents on the β - carbon and α carbon respectively; (c) steric influences.

Scheer et al[126] studied several polar β substituent effects and concluded that such substituents had a retarding influence on the rate of the pyrolysis; recent workers in the subject have gone further and suggested that the deceleration is due to - I inductive withdrawal through σ bonds.[136] The difficulty which arises when considering substituent effects lies in determining the mechanism by which that effect has been produced; inductive, mesomeric and steric factors or a combination of these. Taylor et al,[135] measured the elimination rates for several 2 - substituted ethyl acetates and 3 - substituted propyl acetates and found that conjugative effects of β - substituents were important in the overall rate of pyrolysis; by insulating the substituent from the β - carbon only an inductive effect could apparently operate and

an acceleration in the rate was noted. In the same study, the activating effect of β - alkyl substituents was investigated and was rationalised in terms of steric acceleration, a proposal that has since been confirmed by other workers.[136]

PART 3

SODIUM BOROHYDRIDE REDUCTION OF CARBONYL COMPOUNDS

Many investigations have been carried out to examine the effects of structure upon the reactivity of aldehydes and ketones by determining the rates of reaction of these compounds with reagents such as hydroxylamine,[137] semicarbazide[138] and phenylhydrazine.[139] However, subsequent kinetic studies of oxime and semicarbazone formation revealed that the mechanisms involved complex kinetics not suitable for the study of structural effects.[140] The discovery of sodium borohydride,[141,142] $NaBH_4$, a reducing agent with similar properties but greater selectivity to lithium aluminium hydride, enabled such topics to be examined. Stoichiometrically, one mole of $NaBH_4$, which is a white crystalline solid of remarkable stability, reacts with four moles of carbonyl compound and the reaction has been formulated as :-[142]

$$4R_2CO + NaBH_4 \longrightarrow NaB(OCHR_2)_4$$

$$NaB(OCHR_2)_4 + 2NaOH + H_2O \longrightarrow Na_3BO_3 + 4R_2CHOH$$

Early reduction studies were carried out in water or methanol/water mixtures but once it was realised that these solvents reacted with the hydride agent, liberating hydrogen, isopropyl alcohol replaced them in kinetic measurements.[143]

The kinetics observed by Garrett and Lyttle[144] in the reduction of 3α- hydroxy - 11 α - acetoxy pregnan - 20 - one were bimolecular with respect to the concentration of both the carbonyl compound and sodium borohydride. This is consistent with the

mechanism proposed by Chaikin and Brown[142] of a 1:4 adduct prior to hydrolysis; the adduct would be formed in four successive steps, the first of which would be the slow rate determining transfer of the first hydride ion to the carbon atom of the carbonyl, followed by the rapid replacement of the remaining hydrogens by alkoxy residues.

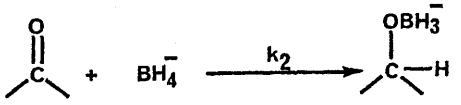
$$R_2CO + BH^-_4 \longrightarrow (R_2CHO)BH^-_3$$

$$R_2CO + (R_2CHO)BH^-_3 \longrightarrow (R_2CHO)_2BH^-_2$$

$$R_2CO + (R_2CHO)_2BH^-_2 \longrightarrow (R_2CHO)_3BH^-$$

$$R_2CO + (R_2CHO)_3BH^- \longrightarrow (R_2CHO)_4B^-$$

The above hypothesis was confirmed by preparation of the intermediate sodium tri-isopropoxyborohydride $NaHB\left[OCH(CH_3)_2\right]_3$ and the demonstration that its reaction with acetone was much faster than the reaction of the ketone with $NaBH_4$ itself.[145] An alternative sequence of events proposed by Garrett and Lyttle is not ruled out by this result.[144] The initial rate determining step may be represented by two possible pathways shown below (fig.11).[146]



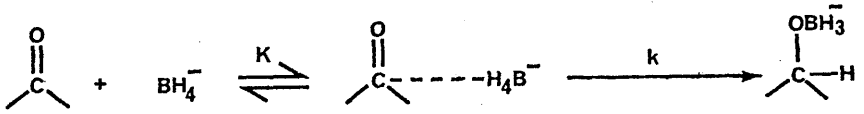


Figure 11.

In an early structure - reactivity study on the reduction of the four ketones - acetone, methyl ethyl ketone, methylisopropyl ketone and methyl t-butyl ketone - , Brown[143] noted the decrease in rate of reaction as steric hindrance increased close to the reaction centre. Irrespective of the mechanism of the rate determining step, the observed rate changes appear to be simply related to the structure of the molecules and Brown believed that borohydride reductions could be a useful tool for investigating the reactivity of the carbonyl group.

Polar and steric influences were considered to be the dominant factors determining the reaction rates for a series of alkyl and aryl carbonyl compounds;[146] the decrease in rate from acetone to acetophenone and benzophenone was in agreement with the greater steric requirements of the aryl groups and their ability to conjugate with the carbonyl and reduce its polar nature. Similarly, the marked increase in the rate on going from acetophenone to benzaldehyde was in accord with the proposed differences in the inductive and steric effects of the methyl compared to hydrogen.

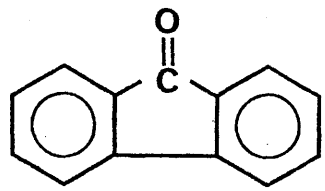
A study of cyclanones[147] revealed a dependence of reactivity upon the ring size and was attributed to changes in internal strain which were greatest for cyclobutanone and hence accounted for its enhanced reactivity. Comparison of the equilibrium data for the dissociation of the comparable cyanohydrins with the rate data for the borohydride reaction revealed a reasonably good linear relationship. This correlation is unexpectedly good for a system of this kind; Brown[147] has stated that in general, linear free energy relationships as described by Hammett[140] for <u>meta</u> and <u>para</u> aromatic derivatives are rarely encountered in other than rigid aromatic systems.

Presumably then, the two reactions must have similar requirements to account for the correlation.

Mesomeric effects were effectively neutralised by attaching phenyl groups to an isolating methylene moiety in a series of α - phenyl acetones;[148] the observed rate increase, by a factor of 2, on going from acetone to α - phenyl acetone was attributed to the electron-withdrawing inductive effect, -I, of the aromatic ring. Further phenyl substitution of the α carbon resulted in a decrease in the rate accounted for by increased steric hindrance which counteracted the favourable electronic effect. A marked rate decrease of 191 was noted for 1,1,1-triphenyl acetone consistent with the proposed dominant steric effect.

4 - substituted cyclohexanones[149] afforded the opportunity to investigate the role of polar contributions in the borohydride reduction of ketones; a Hammett correlation between log k and σ_I, the inductive effect of the substituent, was obtained with a ρ value of +2.78 which confirmed the nucleophilicity of the reaction. It has subsequently been found that substituted alkyl derivatives which showed an enhanced reactivity in this system, did so, predominently, by a conformational effect.[150]

A series of twelve, 2 and 3 substituted fluorenones[151] was reduced and analysis gave a linear Hammett σρ plot using <u>meta</u> and <u>para</u> σ constants; the reaction constant value of +2.65 re-confirmed the character of the rate determining step as involving a nucleophilic attack resulting in a negatively charged transition state.



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Fluorenone 12 is ~ 5 times as reactive as benzophenone; this is consistent with the postulate[152, 153] that the more rigid the structure of a ketone the more reactive it is in carbonyl addition reactions. The good Hammett plots for reduction are in contrast with the lack of correlation with the same system[152] and substituted benzophenones[154] for oxime formation. Complex kinetics and pH dependence are cited as the factors producing non-linearity in the latter. Further work on 2[155] and 4 - substituted fluorenone[156] reductions exhibited similar reaction constants.

Polar substituent effects were investigated in the reaction of acetophenone and nine meta - and para - substituted acetophenones with sodium borohydride.[157] Bowden considered this system to be more suitable than the fluorenones and benzophenones since it lacked an interannular link to complicate the polar effects and steric interactions between the aromatic rings. Application of the Hammett equation gave a good correlation with ρ 3.06 and correlation coefficient of 0.99.

Although Brown[143,146,147] was sceptical regarding the separation of polar and steric effects, Taft proposed[158] an equation to correlate reaction systems involving dependence on both polar and steric effects :-

$$\text{Log } (k/k_o) = \rho^* \sigma^* + \delta E_s$$

where σ^* and E_s are the polar and steric substituent constants respectively and ρ^* and δ are the polar and steric reaction constants respectively. When this treatment was employed to the data relating to the reduction of methyl ketones[147,148] by $NaBH_4$, an excellent correlation resulted ($r = 0.998$).[157]

A study on the effect of structure in bicyclic systems on reactivity,[159] which employed sodium borohydride reduction as the investigative tool, revealed that the rates of reduction were greatly influenced by steric factors (steric approach control); this is in constrast to the corresponding reductions of acyclic and monocyclic systems which are influenced primarily by thermodynamic factors (product development control).

More recently, systems involving $\alpha\beta$ unsaturation have been investigated; although the kinetics are complicated by the possibility of 1,2 and 1,4 additions, studies such as that undertaken by Cockerill[160] on 1,5 - diarylpenta - 1,4 - dien - 3 - ones yield good correlations.

Besides extending the study on acetophenones to include electron releasing groups such as dimethylamino, Morgan[161] measured the substituent effects in a series of acetyl-furans, pyrroles and thiophenes and found a good fit with the Ykawa - Tsuno equation.

The concept of steric approach control and product development control introduced by Dauben,[162] has been extensively employed to rationalise the stereochemistry exhibited by borohydride reduction of ketones, particularly cyclohexanones. The basic difference between

the two postulates is the position of the transition state along the reaction coordinate. If the steric interactions in the transition state are of the long range type between the attacking reagent and the substrate molecule, in its ground state geometry, then an early transition state is proposed; in contrast, a late transition state relates to product-like steric interactions. Detailed investigation of the transition state geometry in the rate limiting step, both by substituent effect studies and kinetic isotope studies reveals a lack of agreement in the results. A contributing factor in this controversy is that in deuterium-labelled experiments 2^{ndy} kinetic isotope effects may contribute to the overall effect, making any assumption concerning the primary effect rather tenuous. Recent studies have avoided this problem by using tritium-labelled borohydride[163] where only low atom percent of tritium is present. Gold et al[164] report that in the reduction of benzaldehyde by tritiated sodium tetrahydridoborate in DMSO and DMSO/H_2O mixtures incorporation of tritium into the aldehyde group of unchanged benzaldehyde occurs; this implies that the hydride transfer step is reversible. The authors go on to postulate that the equilibration process must precede the formation of a stable boron - oxygen bond on thermodynamic grounds.

EXPERIMENTAL

^{1}H N.M.R. spectra were recorded on a Varian T-60 instrument with $CDCl_3$ solutions containing tetramethylsilane as an internal standard. Assignments are in p.p.m. downfield from tetramethylsilane.

^{13}C N.M.R. spectra were recorded at natural abundance with a Varian XL-100 spectrometer, operating in the pulse Fourier Transform mode. The spectra were determined with $CDCl_3$ solutions, containing tetramethylsilane as an internal standard. Proton-noise decoupling was carried out with a wideband noise decoupler.

I.r. spectra were recorded with Perkin-Elmer 257 and Pye-Unicam SP3-100 spectrophotometers.

Mass spectra were recorded on a G.E.C. - A.E.I. M.S.12 spectrometer. The molecular ion (M^+) is quoted first in all cases.

Microanalyses were carried out by Mrs. W. Harkness, Mrs. K.Coombe and Miss D. McKillop in the Microanalytical Laboratory at the University of Glasgow.

Thin layer chromatography (t.l.c.) was carried out using Kieselgel G. (Merck) for analytical purposes and Kieselgel HF_{254} for preparative work; eluants are quoted in brackets.

M.p.s. were recorded on a Kofler hot-stage apparatus and are uncorrected.

Unless otherwise stated, petrol refers to the fraction boiling between 40 - 60°C.

Abbreviations:

br	-	broad
d	-	doublet
m	-	multiplet (in N.M.R.)
		medium intensity absorption (in I.R.)
q	-	quartet
s	-	singlet (in N.M.R.)
		strong intensity absorption (in I.R.)
t	-	triplet
w	-	weak intensity absorption (in I.R.)

PART I

PREPARATION OF 4-SUBSTITUTED CAMPHORS

4-Ethynyl Camphor 13

A solution of camphor (5g, 0.03 mol) in tetrahydrofuran (20ml, freshly distilled from lithium aluminium hydride) was added with stirring from a pressure equalising dropping funnel to a solution of lithium acetylide ethylene diamine complex (Aldrich) (8.0g, 0.08 mol) in dry tetrahydrofuran with the whole system under an atmosphere of argon. After 36 h. at room temperature the reaction mixture was worked up by pouring into ice-water and extracting with ether. Ethereal extracts were dried ($MgSO_4$) and after filtration and evaporation, the product was purified by column chromatography on alumina (15% anhydrous ether/petrol) giving 2 ethynyl-borneol (5.2g, 88%), m.p. 52 - 54°C (lit.[165] 55°C), νmax (nujol) 3610 (br), 3360 (br), 3300 (m), 2100 (w) cm^{-1}.

2 ethynylborneol (10.2g, 0.057 mol) was stirred with trichloroacetic acid at 60° for 4 days when the reaction mixture was worked up in the usual way[104] to give crude trichloroacetate. m.p. 75 - 75°C (lit.[165] 75°C), νmax (nujol), 3300 (m), 2100 (w), 1760 (s), 1245 (s) cm^{-1}. Column chromatography on alumina (40% ethylacetate/petrol) gave 4-ethynylisoborneol, which on purification by sublimation gave white crystals m.p. 85 - 90°C, νmax (nujol) 3400 (br), 3300 (m), 2100 (w) cm^{-1}, δ($CDCl_3$), 3.7 (1H, m); 2.16 (1H, s); 1.06 (3H, s); 0.90 (3H, s); 0.81 (3H, s); 1.2 - 2.5 (7H, m).

Oxidation of the isoborneol with Jones reagent in the usual way[104] gave 13, which was purified by column chromatography (25% ethyl acetate/petrol) followed by sublimation. M.p. 115°C (lit.[165] 115°C), ν_{max} (nujol) 3300 (m), 2100 (w), 1750 (s) cm^{-1}, $\delta(CDCl_3)$, 0.9 (3H, s); 0.95 (3H, s); 1.0 (3H, s); 1.4 - 2.7 (6H, m); 2.25 (1H, s).

4-Ethenyl Camphor 14

4-ethynyl camphor (336mg, 1.9 mmol.) in ethyl acetate (20ml) was hydrogenated in the presence of poisoned catalyst (100mg of Pd. on $BaSO_4$ catalyst poisoned with 130mg of quinoline (redistilled)[166]). After 1 equivalent had been taken up (45 min.), the solution was filtered on a celite column, acidified to pH3, washed several times with water and dried ($MgSO_4$) to yield 328mg of crude product after removal of solvent. Purification was then effected by column chromatography on alumina (7% anhydrous ether/petrol). M.p. 40 - 49°C, ν_{max} (film), 3080 (m), 1745(s), 1635(m) and 910(s) cm^{-1}, $\delta(CDCl_3)$, 0.7 (3H, s); 0.84 (3H, s); 0.94 (3H, s); 1.1 - 2.6 (6H, m); 4.8 - 5.4 (2H, m); 5.6 - 6.2 (1H, m). M^+, 178.

4-Formyl Camphor 15

4-ethenyl camphor (310mg, 1.7 mmol.) dissolved in ethyl acetate (50ml) was treated with ozone at -30°C for 25 min. with stirring. To the resulting solution was added zinc powder (500mg) and acetic acid (1ml.) and the mixture was allowed to stir overnight. After

filtration, the solution was washed with aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and removal of the solvent gave crude 15 (223 mg.), m.p. >220°, ν_{max} (nujol), 2700 (w), 1750 - 1680 (br), $\delta(CDCl_3)$, 0.9 (3H, s); 0.95 (3H, s); 1.1 (3H, s); 1.2 - 3.1 (6H, m); 10.0 (1H, s). Recrystallisation from a petrol (60 - 80°)/ethanol mixture gave a sample which had a large m.p. range and a microanalysis which was inconsistent with the proposed structure. The appearance of a broad absorption (3300 - 2500 cm^{-1}) in the i.r. spectrum indicative of a carboxylic acid, suggested the aldehyde function was being oxidised to the corresponding acid. The sample was allowed to oxidise completely. (Found C, 67.27; H, 8.24. $C_{11}H_{15}O_3$ requires C, 67.32; H, 8.22%).

4-Phenyl Camphor 16

2-phenylisoborneol was prepared by the literature method[167] from camphor (75g, 0.5 mol.). 2-phenylisoborneol was stirred with trichloroacetic acid at 80° overnight, and the mixture was worked up in the usual way[104] to give crude trichloroacetate which was taken through to the next stage, directly. Hydrolysis afforded crude 4-phenyl isoborneol which was recrystallised from petrol (80 - 100°), m.p. 113 - 115°C (lit.,[168] 115°C).

Oxidation, in the usual way,[104] employing Jones reagent gave 16, which was purified by recrystallisation from petrol (80 - 100°), m.p. 66 - 68°C (lit.[168] 67.5 - 68°C), ν_{max} 1740(s), 1600 (w), 1580 (w) cm^{-1}, $\delta(CDCl_3)$ 0.72 (3H, s); 0.87 (3H, s); 1.0 (3H, s); 1.1 - 3.2 (6H, m); 7.45 (5H, s).

4-Ethyl Camphor 17

4-ethynyl camphor (400mg., 2.2 mmol.)in ethyl acetate (20ml) was hydrogenated in the presence of Pd on $BaSO_4$ catalyst. The resulting mixture was filtered on a celite column, dried ($MgSO_4$) and removal of the solvent gave crude 17 which was purified by column chromatography on alumina (20% anhydrous ether/petrol), m.p. 35 - 36°C (lit.[169] 34 - 36°C), ν_{max} (film) 1745 (s) cm^{-1}, $\delta(CDCl_3)$, 0.7 (3H, s); 0.85 (3H, s); 0.9 (3H, s); 0.8 - 1.0 (3H, t); 1.4 - 1.6 (2H, q); 1.2 - 1.8 (4H, m); 1.96 (2H, s).

4-Dimethylamino Camphor 18

The precursor, 4-amino camphor was obtained from camphor-4-urethane[170] using the method of Houben.[171]

To a stirred solution of 4-amino camphor (2.2g, 0.013 mol.) in 90% formic acid (5.12g, 0.1 mol.) was added formalin (4.5ml., 0.06 mol.) and the mixture heated to reflux temperature whereupon CO_2 gas was evolved.[172] After cessation of gas evolution, the reaction mixture was refluxed for a further 8h. On cooling, 3N hydrochloric acid (20ml.) was added and the resulting solution evaporated to dryness under reduced pressure. The pale yellow residue was dissolved in water and the organic base was liberated by the addition of 18N NaOH (30ml.). The methylated amine 18 was taken up in ether, dried ($MgSO_4$) and removal of the solvent gave an analytical sample of the oil (2.1 g, 82%), ν_{max} (film) 2830 (w), 1740 (s) cm^{-1}, $\delta(CDCl_3)$, 0.9 (6H, s); 1.05 (3H, s); 1.2 - 2.3 (6H, m); 2.4 (6H, s). (Found C, 73,7; H, 10.80; N, 7.20. $C_{12}H_{21}NO$ requires C, 73.79; H, 10.84; N, 7.17%).

4-Cyano Camphor 19

Camphene-1-carboxamide (15g, 0.084 mol.), prepared by the method of Bergmann et al,[173] was stirred with acetic anhydride (26g, 0.25 mol.) and pyridine (2 drops) for 100h. at 120°C. On cooling, the mixture was treated with sodium bicarbonate solution until neutral, taken up in ether, washed successively with dilute acid, water, sodium bicarbonate solution, water and dried ($MgSO_4$). Removal of solvent gave a yellow oil (12g.), which was purified by column chromatography on alumina (5% anhydrous ether/petrol) and recrystallisation from ethanol afforded pure 1-cyano camphene, m.p. 39.5 - 40.5°C, νmax (nujol) 2230 (m), 1655 (m), 890 (s) cm^{-1}, δ($CDCl_3$), 1.1 (6H, s); 1.5 - 2.3 (7H, m); 4.9 (1H, s); 5.3 (1H, s). (Found C, 81.7; H, 9.1; N, 8.4. $C_{11}H_{15}N$ requires C, 81.94; H, 9.38; N, 8.69%).

1-cyano camphene (8.5g, 0.053 mol.) was stirred with trichloroacetic acid (22.4 g, 0.14 mol.) at 80° for 50h. when the reaction mixture was worked up in the usual way[104] to give crude trichloroacetate. Base catalysed hydrolysis, using KOH in methanol gave the isoborneol which was oxidised with Jones reagent in the normal manner.[104] Recrystallisation from petrol (80 - 100°) gave pure 19, (5.7g, 39%), m.p. 214 - 215°C (sealed tube), ν_{max} (nujol) 2220 (m), 1750 (s) cm^{-1}, δ($CDCl_3$), 0.95 (3H, s); 1.0 (3H, s); 1.15 (3H, s); 1.5 - 3.8 (6H, m). (Found C, 74.69; H, 8.67; N, 7.99. $C_{11}H_{15}ON$ requires C, 74.54; H, 8.53; N, 7.90%).

4-Iodo Camphor 20

Camphor hydrazone was prepared by the method of Reusch[174] and recrystallised from petrol (80 - 100°) to give white crystals which melted at 53 - 55°C (lit. 55°C). These were used within a day of preparation owing to their hygroscopic nature.

To a stirred solution of camphor hydrazone (10g, 0.06 mol.) in anhydrous ether (30 ml.) and triethylamine (70 ml.) was added, slowly, a saturated solution of iodine in anhydrous ether (>30g of iodine to 200ml. ether).[175] On completion of the reaction, as judged by the cessation of nitrogen evolution and the persistence of the iodine colour, the mixture was diluted with ether (200 ml.), and washed consecutively with 5% sodium thiosulphate solution, 3N HCl, brine, sodium carbonate solution and brine. After drying ($MgSO_4$) and evaporation of the solvent, a dark brown oil, 14.5g, was recovered. Purification on an alumina column (petrol) gave 1-iodo camphene as a colourless oil, (5.7 g, 36%), ν_{max} (film) 1662 (w), 1145 (m), 975 (m), 952 (s), 895 (s) cm^{-1}, $\delta(CDCl_3)$, 1.1 (3H, s); 1.15 (3H, s); 1.8 - 2.5 (7H, m); 4.8 (1H, s); 5.2 (1H, s).

1-iodo camphene (5.3 g, 0.02 mol.) was stirred with trichloroacetic acid (14g, 0.087 mol.) at 80°C for 21h. and under a nitrogen atmosphere. Conventional work-up[104] afforded the crude trichloroacetate (8.2g).

To a vigorously stirred solution of the trichloroacetate in methanol was added a solution of potassium carbonate (1 equiv. in minimum amount of water). After stirring overnight, the reaction mixture was poured into water, extracted with ether and washed several times with brine. Ethereal extracts were dried ($MgSO_4$) and

after filtration and removal of solvent the crude isoborneol was recovered. Recrystallisation from petrol (80 - 100°) gave pure 4-iodo isoborneol, (5.3 g, 94%) m.p. 136 - 138°C (sealed tube).

Jones oxidation of the isoborneol gave 20 which was recrystallised from ethanol, m.p. 157 - 159°C (sealed tube), ν_{max} 1745 (s) cm^{-1}, $\delta(CDCl_3)$, 0.87 (3H, s); 0.96 (3H, s); 1.08 (3H, s); 1.2 - 3.1 (6H, m). (Found C, 43.13; H, 5.38; I, 45.61. $C_{10}H_{15}IO$ requires C, 43.18; H, 5.44; I, 45.63%).

4-Acetoxy Camphor 21

The procedure of Libman et al[176] was employed to prepare the diester, exo-2, 4 bis-trichloroacetoxybornane from camphor, trichloroacetic acid and trichloroacetic anhydride. Subsequent saponification and recrystallisation from ethanol gave the diol, 4-hydroxy isoborneol, m.p.> 220°C (sublimes), νmax (nujol) 3330 (br) cm^{-1}, $\delta(CDCl_3)$ 0.8 (3H, s); 0.91 (3H, s); 1.0 (3H, s); 1.5 - 3.0 (6H, m); 3.7 (1H, m).

Oxidation of the diol by the normal method[104] afforded 4-hydroxy camphor, m.p. 248 - 250°C (lit.,[171] 250°C).

4-hydroxy camphor (700 mg, 4 mmol.) was stirred with acetic anhydride (5g, 0.048 mol) and pyridine (1 drop) at 110°C, overnight. On cooling, the reaction mixture was treated with sodium bicarbonate solution until neutral, taken up in ether and washed consecutively with dilute hydrochloric acid, water, sodium bicarbonate solution, and brine. Drying and removal of solvent gave a yellow oil which, on purification by column chromatography (50% ethyl acetate/petrol),

afforded 21, (450mg, 48%) m.p. 35 - 38.5°C, ν_{max} (film) 1740 (br), 1240 (s) cm^{-1}, $\delta(CDCl_3)$ 0.86 (3H, s); 0.94 (3H, s); 1.00 (3H, s); 1.1 - 3.1 (6H, m); 2.1 (3H, s). M^+, 226.

4-Methoxy Camphor 22

To a stirred slurry of sodium hydride (283 mg, 5.9 mmol., 50% dispersion in oil) in freshly distilled tetrahydrofuran (10 ml.) was added, via a pressure equalising dropping funnel, 4-hydroxy camphor (1g, 0.0059 mol.) in tetrahydrofuran (30 ml.). The resulting solution was stirred overnight under an inert atmosphere. Addition of methyl iodide (3.35g, 0.024 mol) in tetrahydrofuran (20 ml.) via a dropping funnel, resulted in a homogeneous solution which was allowed to stir overnight. The reaction mixture was worked up by pouring into heavily salted water and extraction into ether. The ethereal layer was washed twice with brine, dried ($MgSO_4$). Evaporation of solvent gave crude 22, which was purified by column chromatography (50% ethyl acetate/petrol), (760mg, 70%) m.p. 35 - 39°C, ν_{max} 2820 (w), 1740 (s) cm^{-1}, $\delta(CDCl_3)$ 0.8 (3H, s); 0.93 (6H, s); 1.0 - 2.2 (4H, m); 2.3 (2H, s); 3.34 (3H, s). M^+, 182.

4-(1'1'-dimethyl 2'-acylhydrazide) Camphor 23

To a solution of N,N-dicyclohexylcarbodiimide (4.1g, 0.02 mol) and 1,1-dimethylhydrazine (1.2g, 0.02 mol) in methylene chloride (80 ml) was added camphor 4-carboxylic acid (3.9g, 0.02 mol) at ice-bath temperature.[177] The reaction mixture was stirred overnight at room temperature and the N,N-dicyclohexylurea was removed by filtration. The filtrate was extracted three times with 25ml. aliquots

of 3N HCl, and the combined acid extracts were made basic with sodium carbonate. Extraction with chloroform and evaporation of the dried solvent gave crude 23 (1.2g), $\delta(CDCl_3)$ 0.95 (3H, s); 1.0 (3H, s); 1.08 (3H, s); 1.2 - 3.1 (6H, m); 2.75 (6H, s); 6.66 (1H, br).

4-(1',1',1'-trimethylammonio 2'-acetimide) Camphor 24

To a stirred solution of 23 (1.2 g, 5 mmol.) in the minimum amount of chloroform was added methyl iodide (2g, 0.014 mol); the resulting mixture was allowed to stir for 36 h. Removal of solvent and excess methyl iodide under reduced pressure afforded the hydrazide salt (1.63g).

To the dry salt was added 1N sodium hydroxide (4.4 ml) followed by the extraction of the aqueous solution with chloroform (4 x 250 ml). Gravity filtration of the chloroform washings and removal of the solvent gave the trimethylammonio ylide, 24 which was purified by recrystallisation from ethyl acetate (1.2g, 94%), m.p. 147 - 149°C, νmax ($CHCl_3$), 1731(s) 1570(s) cm^{-1}, $\delta(CDCl_3)$, 0.85 (3H, s); 0.88 (3H, s); 1.0 (3H, s); 1.2 - 3.1 (6H, m); 3.33 (9H, s). (Found C, 66.55; H, 9.78; N, 11.06. $C_{14}H_{24}O_2N_2$ requires C, 66.63; H, 9.59; N, 11.10%).

4-(N-acyliminosulpurane) Camphor 25

To a stirred slurry of camphor 4-carboxamide (2.5g, 0.013 mol) in dimethylsulphoxide (1.5 ml, 0.02 mol) and methylene chloride (20 ml), at -60°C, was added trifluoroacetic anhydride (2.8 ml, 0.02mol) with the temperature maintained below -50°C.[178]

After 3h. the reaction mixture was allowed to warm to room temperature when ether (10ml) and water (30ml) were added. The resulting solution was neutralised with sodium bicarbonate and extracted with chloroform (4 x 60ml). The gravity filtered solvent was removed to yield crude 25 (3g). Recrystallisation from ethyl acetate gave pure ylide (2.5g, 76%), m.p. 109 - 111.5°C, ν_{max} ($CHCl_3$), 1734(s), 1555(s) cm^{-1}, $\delta CDCl_3$), 0.85 (3H, s); 0.93 (3H, s); 1.0 (3H, s); 1.35 - 2.18 (6H, m); 2.66 (6H, s). (Found C, 61.23; H, 8.40; N, 5.45. $C_{13}H_{21}O_2NS$ requires C, 61.14; H, 8.29; N, 5.48%).

PART 2

PREPARATION OF 4-SUBSTITUTED ISOBORNYL ACETATES

Isobornyl Acetate 26

26 was prepared from isoborneol by stirring with an excess of acetic anhydride and a trace of pyridine at 125°C for 12 h. After neutralisation with sodium bicarbonate solution, the product was extracted with ether, washed with brine and dried ($MgSO_4$). Filtration and removal of solvent afforded crude isobornyl acetate which was purified by column chromatography.

4-Phenyl Isobornyl Acetate 27

4-phenyl isoborneol was prepared from 2-phenylisoborneol[167] by a similar method to that employed for 4-nitro isoborneol.[85] The alcohol had m.p. 114 - 115°C (lit.[168] 115.5 - 116°C) and the corresponding acetate 27, prepared and purified as for 26, m.p. 86 - 87°C (lit.[168] 87°C) after recrystallisation from petrol (80 - 100°).

4-Methyl Isobornyl Acetate 28

4-methyl isoborneol was prepared according to the general literature method[173] from 1-methylcamphene[179] (18.3g, 0.12mol) and trichloroacetic acid (55g, 0.34mol) and subsequent base catalysed hydrolysis of the trichloroacetate. The alcohol (34g, 0.2mol) was esterified by the same method used for 26 and the extent of reaction was monitored by t.l.c. Purification by column chromatography on

alumina (ethyl acetate) gave an oil, 28, (33g, 78%), ν_{max} (film) 1740(s), 1235(s) cm^{-1}, $\delta(CDCl_3)$, 0.7 (3H, s); 0.87 (3H, s); 0.9 (3H, s); 1.1 - 1.9 (6H, m); 2.0 (3H, s); 4.55 - 4.86 (1H, m). (Found C, 74.3; H, 10.70. $C_{13}H_{22}O_2$ requires C, 74.24; H, 10.54%).

4-Nitro Isobornyl Acetate 29

4-nitro isoborneol was prepared by the method of Morris and Murray[85] from 1-nitro camphene (15g, 0.083mol) and the derived acetate 29 was prepared analogously to 26. Purification by column chromatography (ethyl acetate) gave crystals, m.p. 36 - 38°C, ν_{max} (film) 1730(s), 1520(s), 1230(s), 820(s) cm^{-1}, $\delta(CDCl_3)$, 0.9 (3H, s); 1.0 (3H, s); 1.13 (3H, s); 1.3 - 3 (6H, m); 2.05 (3H, s); 4.7 - 4.9 (1H, m). (Found: C, 59.56; H, 7.91; N, 5.72. $C_{12}H_{19}NO_4$ requires C, 59.74; H, 7.94; N, 5.81%).

4-Chloro Isobornyl Acetate 30

4-chloro isoborneol was prepared by the literature method[173] from 1-chloro camphene and the corresponding acetate was prepared and purified as described previously for 26. 30 was obtained as an oil, ν_{max} (film) 1740(s), 1235(s) cm^{-1}, $\delta(CDCl_3)$, 0.86 (3H, s); 0.93 (3H, s); 1.05 (3H, s); 1.2 - 2.6 (6H, m); 2.08 (3H, s); 4.6 - 4.8 (1H, m). Found: C, 62.3; H, 8.5; Cl, 15.6. $C_{12}H_{19}ClO_2$ requires C, 62.47; H, 8.3; Cl, 15.37%).

4-Acetoxy Isobornyl Acetate 31

Exo-2,4,-Dihydroxybornane was obtained by the general method[176,180] from camphor. The diacetate 31 was prepared and purified as described previously for 26, giving a white solid, m.p. 51 - 53°C, ν_{max} (nujol) 1730 (s), 1245 (s) cm^{-1}, $\delta(CDCl_3)$ 0.87 (6H, s); 1.0 (3H, s); 1.2 - 3.1 (6H, m); 2.0 (6H, s); 4.68 - 4.86 (1H, m). (Found: C, 65.94; H, 8.84; $C_{14}H_{22}O_4$ requires C, 66.12; H, 8.72%).

4-Cyano Isobornyl Acetate 32

Camphene-1-carboxamide[173] (18.4g, 0.103 mol) was heated at 80° for 15h with trichloroacetic acid (76g, 0.46 mol). The resulting solution was worked up as described previously[85] to give the trichloroacetate (29.4g, 87.5%) as a very insoluble white solid which was saponified directly with methanol (170ml) and sodium hydroxide (33ml of a 30% aqueous solution) overnight at room temperature. The resulting solution was filtered and the methanol partially evaporated; neutralisation was effected with dilute hydrochloric acid to give the highly insoluble isoborneol 4-carboxamide as a white solid which was recrystallised from ethanol. M.p. 217 - 219°C, ν_{max} (nujol) 3600 - 3200 (br), 1650 (s), 1580 (s), 1030 (m) cm^{-1}. (Found: C, 67.2; H, 9.4; N, 7.13. $C_{11}H_{19}NO_2$ requires C, 66.97; H, 9.71; N, 7.10%).

Isoborneol-4-carboxamide (18.3g, 0.092 mol) was heated with acetic anhydride (29g, 0.27 mol) containing two drops of pyridine at 130° for 120h. The cooled solution was poured into cold aqueous sodium bicarbonate solution and stirred for 3h to hydrolyse excess acetic

anhydride. The solid acetate was taken up in ether, washed with dilute hydrochloric acid, water, brine and dried ($MgSO_4$). After removal of $MgSO_4$ by filtration, the solvent was evaporated to give crude acetate, 18g, as a light brown solid. This was chromatographed on alumina (30% anhydrous ether/petrol) and gave white crystals of 32, (12g, 58%), m.p. 62 - 63°C, ν_{max} (nujol) 2225(m), 1730(s), 1240(s) cm^{-1}, $\delta(CDCl_3)$, 0.92 (3H, s); 0.99 (3H, s); 1.15 (3H, s); 1.2 - 2.4 (6H, m); 2.05 (3H, s); 4.6 - 4.9 (1H, m). (Found: C, 70.68; H, 8.44; N, 6.63. $C_{13}H_{19}NO_2$ requires C, 70.56; H, 8.65; N, 6.33%).

4-Iodo Isobornyl Acetate 72

4-iodo isoborneol was prepared from 1-iodo camphene as previously described in the synthesis of 20. The corresponding acetate, 72, was obtained in the usual way, and purification by column chromatography (ethyl acetate) afforded an oil, ν_{max} (film) 1740(s), 1235(s) cm^{-1}, $\delta(CDCl_3)$, 0.84 (3H, s); 1.0 (6H, s); 1.2 - 2.8 (6H, m); 2.02 (3H, s); 4.6 - 4.8 (1H, m). M^+,322.

4-Ethynyl Isobornyl Acetate 33

4-ethynyl isoborneol was obtained by a modified version of the literature method as described in the preparation of 13. Acetate, 33 was prepared in the usual way and column chromatography (anhydrous ether) gave an analytical sample, m.p. 30 - 32°C, ν_{max} (film), 3300(s), 2100(w), 1740(s), 1235(s) cm^{-1}, $\delta(CDCl_3)$, 0.8 (3H, s); 1.0 (6H, s); 1.2 - 2.4 (6H, m); 2.0 (3H, s); 2.2 (1H, s); 4.6 - 4.8 (1H, m). (Found: C, 76.2; H, 9.29. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%).

Tricyclene 34 was prepared according to a literature method.[181]

Quantitative gas liquid chromatographic analyses were carried out on columns consisting of (i) FFAP 7% - Chromosorb W. AW. DMCS. 80 - 100 mesh, and (ii) Carbowax 20M 15% - Chromosorb W. AW. DMCS. 80 - 100 mesh. Esters 26, 28, 29, and 30 were distilled several times until a purity of greater than 97.8% was obtained by g.l.c. analysis.

RATE MEASUREMENTS

The pyrolysis experiments were performed in a static system, and the reaction vessel was at all times seasoned by the product of allyl bromide decomposition.[182, 183] The kinetic measurements were made by titration of acetic acid produced in the reaction against a solution of 0.05N sodium hydroxide.

The esters were injected directly into the reaction vessel through a silicon rubber septum.[184] The low melting solid esters 29 and 31 were kept in liquid form by gentle warming in order to introduce them into the reaction vessel through injection. The temperature of the pyrolysis reactions was kept constant, within $\pm$ 0.2°C as measured by a calibrated platinum/platinum - 13% rhodium thermocouple. Measurements at different points along the reaction vessel showed no temperature gradient.

PART 3

The 4-substituted bornanones, 13, 16, 18, 19 and 22 were prepared as already described.

4-Methyl Camphor, 35 was prepared according to the general literature[173] method from 1-methyl camphene (5g, 0.033 mol). Column chromatography, on alumina, of the crude product gave pure 35 (3g, 74%), m.p. 167 - 169°C, (lit.,[185] 167 - 168°C), ν_{max} 1745 (s) cm^{-1}.

4-Chloro Camphor, 36 was prepared by the literature method[173] from 1-chloro camphene (5g, 0.03 mol). Recrystallisation from ethanol gave 36 (3.4g, 60%), m.p. 196 - 197.5°C (lit., 198 - 199°C).

Camphor-4-Carboxylic Acid 37 was obtained by the method of Bergman et al[173] from camphene-1-carboxylic acid (5g, 0.027 mol) to give after recrystallisation from ethanol pure 37 (3g, 55%), m.p. 238 - 239°C (lit., 239 - 240°C).

4-Nitro Camphor 38 was prepared according to the literature method[173] from 1-nitro camphene (5g, 0.027 mol). Recrystallisation of the crude product from ethanol gave pure 38, (4g, 75%). m.p. 220 - 221°C, (lit., 220 - 221°C).

RATE MEASUREMENTS

The kinetic runs were carried out in a solvent consisting of dioxan (2ml), water (0.5ml) and sodium hydroxide (0.5ml, 0.1N). A 0.6M solution of sodium borohydride was prepared and standardized by the iodate method of Lyttle et al;[186] the standard solution was then thoroughly degassed.

The rate of reaction was determined spectrophotometrically at 25.5°C by monitoring the appropriate wavelength at which the ketone absorbed (Table [10]).

The kinetics were carried out by placing in the reference cell, 1 ml of the sodium borohydride solution plus 1 ml of solvent and in the reaction cell, 1 ml of the sodium borohydride solution plus 1 ml of a 0.2M solution of ketone in the reaction solvent. Timing commenced as the ketone was added to the reaction vessel. Measurements of the optical density at the suitable wavelength for the ketone gave concentration values.

MISCELLANEOUS PREPARATIONS

4-(3-Hydroxy, 3-methylbut-1-ynyl) Camphor 39

A solution of lithium diisopropylamide was prepared from successive addition of diisopropylamine (0.14g, 1.4 mmol.) and n-butyl lithium (0.88 ml, 1.4 mmol. of a 1.6M solution in hexane) to tetrahydrofuran (10 ml, freshly distilled from lithium aluminium hydride) at -70°C followed by stirring for 20 min. To this cold solution maintained under an argon atmosphere was added a solution of 4-ethynyl camphor, 13, (250 mg., 1.4×10^{-3} mol) in tetrahydrofuran via a pressure equalising dropping funnel. After a further 20 min., excess acetone (1 ml, 1.3×10^{-2} mol) was similarly added. The solution was then allowed to reach room temperature and stirring was continued for 4h. The reaction mixture was worked up by pouring into 0.5M hydrochloric acid (50 ml) and extracting with ether (2 x 70 ml). The combined ethereal extracts were washed with brine (3 x 25 ml) and dried ($MgSO_4$) to give, after filtration and removal of ether, an off-white solid (280mg) which on purification by preparative t.l.c. (50% ethyl acetate/petrol) gave 39, (90mg., 27%), Rf (0.6), m.p. 89 - 91°C, ν_{max} (nujol), 3500(s), 2220(w), 1730(s) cm^{-1}, $\delta(CDCl_3)$, 0.8 (3H, s); 0.92 (6H, s); 1.5 (6H, s); 1.2 - 2.8 (7H, m). (Found: C, 76.96; H, 9.67. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%).

4-(3-Acetoxy, 3-methylbut-1-ynyl) Camphor 40

4-(3-hydroxy, 3-methylbut-1-ynyl) camphor, 39, (80 mg, 0.34 mmol.) was heated at 110°C for 5 days with excess acetic anhydride (10 ml) and pyridine (1 drop). The reaction mixture was then poured into cold sodium bicarbonate solution and stirred overnight. The acetate was

taken up in ether which was washed consecutively with dilute hydrochloric acid, brine, sodium bicarbonate solution and brine (x2); after drying ($MgSO_4$), filtration and removal of ether gave 40 which was purified by preparative t.l.c. (30% ethyl acetate/petrol). Rf (0.6) (87mg, 92%) m.p. 61 - 64°C, ν_{max} (nujol) 2220(w), 1740(s), 1240(s) cm^{-1}, $\delta(CDCl_3)$, 0.83 (3H, s); 0.90 (3H, s); 0.97 (3H, s); 1.63 (6H, s); 2.0 (3H, s); 1.2 - 2.8 (6H, m). (Found: C, 73.72; H, 8.91. $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%.

4-(3-Methoxy, 3-methylbut-1-ynyl) Camphor 41

To a solution of 4-(3-hydroxy, 3-methylbut-1-ynyl) camphor, 39, (146mg, 0.6 mmol.) in tetrahydrofuran (5ml, freshly distilled from lithium aluminium hydride), under argon, at -70°C, was added n-butyl lithium (0.387ml, 0.6 mmol. of a 1.6M solution in hexane). After warming up to room temperature and stirring for 1h., a solution of methyl iodide (1.3g, 9 mmol.) in dry tetrahydrofuran was added, via a pressure equalising dropping funnel and the resulting solution was stirred overnight. The reaction mixture was worked up by pouring into 0.5M hydrochloric acid (50ml) and extracting with ether (2 x 50ml). The combined ethereal washings were treated with brine (2 x 25ml) and dried ($MgSO_4$) to give, after filtration and evaporation of solvent, an oil (148 mg). Purification by preparative t.l.c. (20% ethyl acetate/petrol) afforded 41, as an oil, Rf (0.5), (90mg, 58%) νmax (film) 2820(w), 2220(w), 1740(s) cm^{-1}, $\delta(CDCl_3)$, 0.85 (3H, s); 0.94 (3H, s); 0.98 (3H, s); 1.45 (6H, s); 1.2 - 2.8 (6H, m); 3.34 (3H, s). M^+ 248.1747, $C_{16}H_{24}O_2$ requires 248.1776.

1-Methoxy Camphene 42

A solution of 1-iodo camphene (1g, 3.8 mmol.) in methanol (110ml, distilled) was irradiated for 6h.[82] Irradiation was conducted with the broad mercury spectrum using a Hanovia 450 - W medium arc immersion lamp placed inside a double-walled, water-cooled quartz immersion well which was itself inside a 120ml pyrex reaction vessel. Agitation of the reaction mixture was effected by an argon flow through the solution which also excluded oxygen from the system. Zinc wool (7g) was present in the reaction vessel as a scavenger for liberated iodine and hydrogen iodide. After irradiation, the methanolic solution was concentrated, diluted with water and extracted with ether (2 x 100 ml). The combined ether washings were treated with 10% aqueous sodium thiosulphate solution (20 ml), brine and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent afforded crude 42 (300mg) which was purified by column chromatography (petrol) to give an oil, (200mg, 32%), ν_{max} (film) 3070(w), 2820(m), 1660(w), 885(s) cm^{-1}, $\delta(CDCl_3)$, 1.02 (3H, s); 1.06 (3H, s); 1.35 - 2.05 (7H, m); 3.38 (3H, s); 4.65 (1H, s); 4.83 (1H, s). M^+, 166.

Reaction of 1-Methoxy Camphene 42 with Trichloroacetic Acid

1-methoxy camphene 42 (1g, 6 mmol.) was stirred with trichloroacetic acid (3g, 1.8×10^{-2} mol) at 80°C for 7h. The reaction mixture was worked up by pouring into cold water, neutralising with sodium bicarbonate and extracting with ether (2 x 50ml). The combined ether extracts were washed with brine, dried ($MgSO_4$) and removal of the solvent gave a solid (800mg) which was purified by column chromatography on alumina

(ethyl acetate) to yield a white crystalline compound 43 (0.75g, 82%) m.p. 175 - 177°C, ν_{max} (nujol) 1745(s) cm^{-1}, $\delta(CDCl_3)$, 0.8 (3H, s); 0.88 (3H, s); 0.92 (3H, s); 1.2 - 2.6 (7H, m).

A compound with identical spectral data was isolated when the photolysis of 42 was carried out in the absence of the iodine scavenger, zinc wool. Preparative t.l.c. (15% ethyl acetate/petrol) of the crude material afforded 43 (150mg, 90%).

Photolysis of 1-Iodo Camphene under Different Reaction Conditions

A solution of 1-iodo camphene (890mg, 3.3 mmol.) in dry methanol was irradiated for 52h. using a Hannovia 450 W medium arc immersion lamp in a double-walled, water-cooled quartz immersion well. The reaction vessel consisted of a 200ml conical flask into which was placed the solution and the immersion well. Neither argon nor zinc wool were employed in the reaction. Work-up was analogous to that for the isolation of 42 and preparative t.l.c. of the crude product (10% ethyl acetate/petrol) gave two bands:-

1) 44, Rf (0.4), 237mg, m.p. 72 - 73°C, ν_{max} (nujol) 1740(s) cm^{-1}, $\delta(CDCl_3)$, 0.9 (3H, s); 1.1 (3H, s); 1.2 - 2.6 (7H, m); 3.0 - 3.5 (2H, AB q). (Found: C, 43.06; H, 5.51; I, 45.97. $C_{10}H_{15}IO$ requires C, 43.18; H, 5.44; 45.63%). M^+ 278.

2) Rf (0.8), 100mg, oil, ν_{max} (film) 1662(w), 1145(m), 975(m), 952(s), 895(s) cm^{-1}, $\delta(CDCl_3)$ 1.1 (3H, s); 1.15 (3H, s); 1.8 - 2.5 (7H, m); 4.8 (1H, s); 5.2 (1H, s).

Reaction of 10-Iodo Camphor 44 with Hydroxylamine

A solution of 44 (146mg, 0.52 mmol.) in ethanol (minimum required) was gently refluxed with a solution of hydroxylamine (150mg, 2.1 x 10^{-3} mol) in water (5ml) and sodium acetate (179mg) for 5h. The reaction mixture was poured into cold water and extracted with ether (2 x 20 ml); the combined organic layers were washed with brine, dried ($MgSO_4$) and removal of the solvent gave crude product (105 mg). Recrystallisation from methanol gave white crystals, 45, (80 mg, 52%) m.p. 162 - 163°C (lit.,[187] 158°C), ν_{max} (nujol) 3360 (br), 1670(w), 920(m) cm^{-1}, $\delta(CDCl_3)$, 0.85 (3H, s); 1.0 (3H, s); 1.2 - 3.0 (7H, m); 3.2 - 3.6 (2H, ABq); 8.5 - 8.9 (1H, br). (Found: C, 40.87; H, 5.48; N, 4.57; I, 43.49. $C_{10}H_{16}IN$ requires C, 41.09; H, 5.14; N, 4.79; I, 43.49%).

Photolysis of 4-Iodo Camphor 20

A solution of 20 (1g, 3.5 mmol.) in dry methanol was irradiated for 40h, employing the same photolysis apparatus and reaction conditions that resulted in the isolation of 44. Preparative t.l.c. (15% ethyl acetate/petrol) after the normal work-up gave two bands:-

1) 22, Rf (0.2), oil, 40mg, νmax (film), 2820 (m), 1740(s) cm^{-1}, $\delta(CDCl_3)$ 0.8 (3H, s); 0.93 (6H, s); 1.0 - 2.2 (4H, m); 2.3 (2H, s); 3.34 (3H, s).

2) 46, Rf (0.1), (300mg 29%), m.p. 107.5 - 108.5°C (Recrystallised from ethyl acetate), ν_{max} (nujol) 3040(m), 1760(s) cm^{-1}, ($CDCl_3$), 0.95 (6H, s); 1.1 (3H, s); 1.5 - 2.2 (4H, m); 3.4 (2H, s). (Found: C, 40.96; H, 5.17; I, 43.19. $C_{10}H_{15}IO_2$ requires C, 40.84; H, 5.14; I, 43.15%). M^+, 294.

4-Iodo Tricyclene 47

A solution of 4-iodo camphor 20, (12g, 0.043 mol.), and p-tolylsulphonylhydrazine (8.02g, 0.043 mol) in the minimum amount of ethanol was refluxed overnight in the presence of concentrated hydrochloric acid (4 drops).[188] On cooling, crystals separated. These were filtered and recrystallised from ethanol to give pure 4-iodo camphor p-tolylsulphonylhydrazone, (13.2g, 69%), m.p. 218 - 219°C, (Found: C, 45.48; H, 5.05; N, 6.20; I, 28.70. $C_{17}H_{23}N_2SO_2I$ requires C, 45.75; H, 5.19; N, 6.28; I, 28.43%).

To a stirred solution of 4-iodo camphor p-tolylsulphonyl hydrazone (13.1g, 0.03 mol) in tetrahydrofuran (100ml, freshly distilled from lithium aluminium hydride) under an inert atmosphere was added, via a pressure equalising dropping funnel, sodium methoxide in methanol (1.84g, 0.08g atom Na).[181] The resulting solution was allowed to stir for 30 min. when the solvent was removed under reduced pressure (water bath temperature $<40^{\circ}C$). The sodium salt remaining was decomposed at 200°C and 47 was swept into a condenser by an argon stream. Column chromatography (petrol) gave pure 4-iodo tricyclene 47, (5g, 65%) m.p. 90 - 90.5°C, ν_{max} (nujol) 3050(w) cm^{-1}, $\delta(CDCl_3)$ 0.8 (6H, s); 0.9 (2H, s); 1.16 (3H, s); 1.5 - 2.25 (4H, ABq). (Found: C, 45.58; H, 5.87; I, 48.16. $C_{10}H_{15}I$ requires C, 45.82; H, 5.77; I, 48.41%).

Reaction of 4-Iodo Tricyclene 47 with m-Chloroperbenzoic Acid

To a stirred solution of 47 (100mg, 0.76 mmol.) in methylene chloride (1.5ml) was added m-chloroperbenzoic acid (82mg, 7.6×10^{-4} mol).[18

After an overnight stir, the reaction mixture was worked up by pouring into sodium bicarbonate solution and extracting with ether (2 x 25 ml). The combined ether washings were treated with brine, dried ($MgSO_4$) and removal of the solvent gave a white solid (120mg), νmax 3050(w), 1650(m), 1290(s), 1260(s), 745(s) cm^{-1}. Preparative t.l.c. (100% ethyl acetate) gave two bands:-

1) Rf (0.8), 25mg, m.p. 89 - 90°C, νmax (nujol) 3050(w) cm^{-1}

2) Rf (0.7), 30mg, m.p. 153 - 156°C, νmax (nujol) 3600 - 3200(s), 3200 - 2400(m), 1690(s) cm^{-1}.

Purification of the crude product by recrystallisation from toluene gave a pure sample, 48, m.p. 178 - 182°C, νmax 3050(w), 1650(m), 1290(s), 1260(s), 745(s) cm^{-1}, δ($CDCl_3$), 1.13 (6H, s); 1.2 (3H, s); 1.35 (2H, s); 2.0 - 2.66 (4H, ABq); 7.23 - 7.85 (8H, m). (Found: C, 50.18; H, 4.07; I, 21.95; $C_{24}H_{23}IO_4Cl_2$ requires C, 50.29; H, 4.04; I, 22.14%).

Reaction of Iodoso Tricyclene Di-meta-chlorobenzoate, 48 with Sodium Hydroxide.

To a solution of 48 (200mg, 0.35 mmol) in methanol (10 ml) was added 3N sodium hydroxide (0.525ml) and the resulting mixture stirred overnight. Concentration of the methanolic solution, and extraction with chloroform afforded 47 (45mg.). Acidification of the remaining aqueous layer and extraction with chloroform gave a white solid (97mg), m.p. 152 - 155°C, νmax (nujol) 3200 - 2400(m), 1690(s) cm^{-1}.

RESULTS AND DISCUSSION

PART I

SUBSTITUENT EFFECTS ON ^{13}C CHEMICAL SHIFTS OF 4-SUBSTITUTED CAMPHORS

Table 2 shows the ^{13}C chemical shifts of 4-substituted camphors 13 - 25, and the corresponding substituent induced chemical shift increments are given in the adjoining table. The assignment of resonances in the ^{13}C nmr spectra of the camphor derivatives 13 - 25, is made in a similar manner to those of other bicyclic systems, and is aided by proton decoupled off-resonance spectra; the methylene C(5) and C(6) signals are distinguished from that of C(7) by the "Grutzner triplets" observed in the off-resonance spectra of the former carbons.

The work presented here, is an extension of a study on a series of 4-substituted camphors which originally comprised of the parent compound plus ten substituted derivatives;[190] the novel camphors included in the current survey were chosen in view of their interesting substituent effects noted in related studies, and their associated inductive power (represented by σ_I) enabling a complementary investigation of the system to be made.

The α-shift observed at C(4) for the camphor series has been likened to that of 4-substituted tricyclenes and 1-substituted adamantanes;[190] the C(1) chemical shifts of the adamantanes has been shown to correlate well[83] with corresponding substituted carbons in t-butyl and cyclohexane derivatives. These, in accord with many other alkyl species exhibit an α-effect which is accounted for, in part, by the electronegativity of the substituent. However, as

noted by Spiesecke and Schneider[21] certain groups produce abnormally high field α shift which cannot be attributed purely to group electronegativity. Into this category falls the heavy halogen, iodine and the cyano and acetylene moieties.[77] The term heavy atom effect, associated with iodine, and to a lesser degree with bromine, was introduced with the discovery of deviations from the linear correlation between the substituent chemical shift and E_R, the electronegativity parameter, especially in iodides.[21,66] This was originally interpreted as an anisotropy effect associated with the halogen;[21] more recently, other postulates have included the intramolecular dispersion of the halogen,[191] steric interaction induced by a variation in molecular geometry,[15] solvent effects,[192] spin-orbital interactions[193] and the presence of d orbitals.[194] A recent study has revealed that the heavy atom effect is not restricted to halogens but also applies to chalcogens such as Se and Te;[195] an excellent correlation exists between the chemical shift of the directly substituted carbon of corresponding chalcogen and halogen derivatives. As expected, the iodo bonded carbon in the present series shows an exceptionally large shielding effect in comparison with the two previously studied halogens.

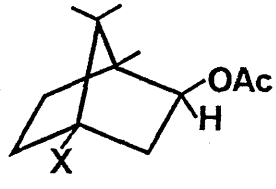
Relatively high field α shifts are produced with substituted cyano and alkyne groups and these have also been attributed to an neighbour-anisotropy effect;[21] low field shifts at the β-carbon accompany the α shielding. It has been argued that an anisotropy effect cannot account for such abnormal shifts, since the ^{13}C shielding shift is an order of magnitude larger than ^{1}H shifts

which would not be the case if an anisotropy effect were operating since it is independent of the nucleus involved.[196] Further evidence which opposes the idea of diamagnetic anisotropy is the failure of the point-dipole approximation of McConnell,[197] which was derived to rationalise quantitatively the proton chemical shift in linear alkynes,[198] to predict the chemical shift of the α-carbons in the same system.[199]

Reasonable correlations which often exist with the α-carbon are frequently absent with β-carbons. The 4-substituted camphors are no exception. Two types of carbon atom are β to the substituent; the secondary carbons C(3) and C(5) and the quaternary carbon C(7). No relationship exists between these chemical shift increments and any single substituent parameter, owing to the complex nature of the substituent effects which influence the chemical shifts of this position.[190] Studies have shown that the α-shielding effect is basically independent of hydrisation of the α carbon but that the magnitude and sign of β-shifts dramatically changes with hybridisation. Substituents which produce anomolous shifts at the α position, namely I, CN and C≡CH, induce large low field shifts at β carbons in accord with the postulate of Spiesecke and Schneider.[21] The smaller β-shifts for C(3) with respect to C(5) noted in previous work[190] continues to appear, even in the above examples and may be due to a damping effect by the carbonyl moiety at C(2).

The γ-shift observed at C(2), the carbonyl carbon shows a reasonable empirical correlation ($r = 0.965$)[190] with the linear free energy parameter, σ_I. Other studies on the γ effect of heteroatomic substituents on carbonyl shieldings in rigid ring systems exhibit

similar relationships but are often complicated by steric factors. Due to the spatial arrangement of the carbonyl moiety and the C(4) substituent few non-bonded interactions are present and this allows the inductive influence to produce paramagnetic shifts. Extrapolation from plot (Fig.12) gives σ_I values for the ylid substituents which indicate electron releasing character. It is interesting to note that the substituents which had been responsible for deviations in the α-shift no longer exhibit unusual behaviour at C(2). This is perhaps merely a consequence of distance from perturber group to perturbed site, or more likely, is due to an over-riding effect which swamps the mechanism that had been responsible for the anomolous α-shift. In a series of 4-substituted isobornyl acetates,[200] 49, a rough correlation exists between σ_I, the inductive power of the substituent and the ^{13}C chemical shift difference for the C(2) carbon; however, the iodo-derivative deviates considerably from this relationship producing a γ-shift smaller than expected (more deshielded). It has been suggested[200] that the polar C - O bond in the acetate acts in a similar but less effective manner than the carbonyl function in camphor in producing large shielding effects at C(2) with remotely substituted electron-withdrawing groups. If this



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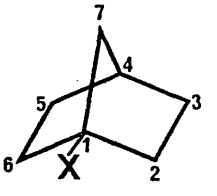
is so, the lack of correlation shown in the acetate series could be accounted for by the small polar shielding effect associated with the C - O bond being opposed by a larger deshielding one originating from the heavy atom effect of iodine. It should be noted that in the same study,[200] the cyano and ethynyl substituted acetates obey the correlation suggesting that their anomolous behaviour is either an order of magnitude smaller than that for iodine or that the mechanism by which it is transmitted is ineffectual over the distance involved. Any proposals to account for the γ shifts in different systems, must take account of changes in hybridisation of the γ carbon which may produce large effects in the carbon shielding; comparison of the isobornyl acetate series with that of the camphors involves a change in hybridisation of the C(2) carbon from sp^3 to sp^2. The C(6) position in both the camphor and isobornyl acetate series are γ to the substituent as well as being sp^3 hybridised, and so perhaps inspection of these positions in the iodo-derivatives would be a more realistic model. In both cases, they are markedly deshielded relative to the unsubstituted parent and compounds with comparable substituents (similar σ_I). In a study of 1-substituted norbornanes 50, Poindexter and Kropp[82] found that positions C(3) and C(5),



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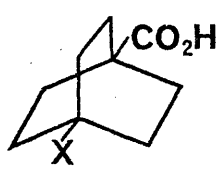
exhibited low field γ shifts attributed in the main to an inductive effect operating via a through bond mechanism. However, the heavy halogens, Br and I induced greater deshielding than their inductive power warranted, substantiating the idea of a γ deshielding effect. Similar results are found in 1-substituted adamantanes[83] and bicyclo [2.2.2.] octanes[84] where the γ carbons are tertiary and secondary respectively. In contrast, the γ shifts for the equivalent C(2) and C(6) carbons of the cyclopropane ring in 4-substituted tricyclenes[85] are to higher field (more shielding) with electron-withdrawing substituents and correlate well with E_R. This contrasting behaviour between the γ-shifts of the tricyclenes and adamantanes has been attributed to many factors, the one most likely perhaps hybridisation. It might be expected that the C(2) and C(6) cyclopropyl carbons of 4-iodo tricyclene would be similarly shielded with respect to the γ carbons of the unsubstituted parent compound which resonate at 20.6 ppm. However, although the iodo cyclopropane carbons do indeed experience shielding (absorb at 20.55 ppm), it is almost cancelled out by the γ deshielding effect of the iodine atom. Clearly then, the absorptions of variously hybridised γ carbons in differing systems show a marked deshielding effect when the perturbing group is iodine. The observed effect is considerably reduced in systems where the γ carbon experiences other shielding factors, which is the situation which arises with iodo isobornyl acetate. It appears that the shielding effect experienced at C(2) in the 4-substituted camphors must dominate the heavy atom γ effect, since the C(2) absorption of C(2) of 4-iodo camphor does not deviate from the correlation

which exists between the γ shifts and σ_I.

Good linear correlations between the ^{13}C shifts of carbonyl carbons in some cyclic and bicyclic ketones[99] and $n \rightarrow \pi^*$ transition energies have been interpreted in terms of a dominant role played by the excitation energy in accounting for the chemical shift variation. Stothers[201] and others have questioned the generality of these correlations and instead proposed that steric interactions, in the form of α-bond eclipsing interactions are largely responsible for carbonyl chemical shifts. Yet other workers[202] have suggested the importance of angle strain; departure from sp^2 hybridisation at the carbonyl bond produced by increased p character of the carbon orbital associated with the C - C linkage leads to an increase of s character in the carbon orbital of the carbonyl group, resulting in a less polar bond. This postulate accounts for the observed increase in the i.r. carbonyl stretching frequency with reduction of ring size in cyclic ketones. Although the alternative mechanisms mentioned may explain specific examples, they cannot be applied generally; in the present series, few of the parameters suggested as important factors in determining the carbonyl chemical shift change sufficiently to account for the observed shift variation. It was noted that the absorptions for the carbonyl carbon were progressively shifted to higher field with increasing electron-withdrawing power of the substituent. This could not be explained in terms of purely an inductive effect since according to Pople's CNDO/2 calculations,[56] the γ carbon should be deshielded by an electron attracting group; attenuation of the effect by a factor of

2.3 per intervening carbon also suggests operation of an alternative effect. Linear electric field[203] contributions have been considered to be responsible for the effect[190] since it is known that ^{13}C shifts associated with these contributions are large in comparison with proton shifts; the introduction of molecular charges or dipoles into the system will further enhance the field effect. The study of dissociation constants of bicyclo [2.2.2.] octane - and bicyclo (2,2,1) heptane-1-carboxylic acids, 51 and 52, substituted at the 4 position gave results which were consistent with a field effect



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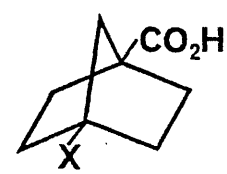

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model, and not representative of an inductive one.[204] The similarity in geometries of these systems with the 4-substituted bornanones suggests that a field effect may be operating; the γ effects noted at the carbonyl in 4-adamantanones[205] and bicyclo [3.2.1] octan-8--ones[206] are said to arise from various factors including a contribution from a through space effect (direct field effect) which results in the polarization of the C=O π bond. High field γ shifts have also been observed in a series of 2-substituted bicyclo [3.3.1] nonan-9-ones[207] and attributed to an interaction between the electron lone pairs of

certain substituents and the π electrons of the carbonyl. The magnitude of the field effect acting in the present series is clearly a function of the polarity of the substituent and the polarisibility of the group at C(2); the γ shifts increase along the series methylene γ carbons < acetate γ carbon < carbonyl γ carbon which indicates the relative polarity of the various functional groups.

Relatively little work has been undertaken to study the influence of molecular structure change on ^{17}O chemical shifts of various functional groups. This lack of data is a consequence of the experimental difficulties associated with accurate measurements of resonance signals for the ^{17}O nucleus owing to its low natural abundance (0.037%) and quadrupolar nature ($I = \frac{5}{2}$). It is known that ^{17}O shieldings are dominated by the paramagnetic contribution which is a function of ΔE and $\langle r^{-3} \rangle_{2p}$ and correlations have been found between these two terms and the ^{17}O chemical shifts in a few series.[100] A study of β-methylated bicyclic ketones[103] revealed that the ^{17}O shieldings were very sensitive to steric factors. It was concluded that an investigation of the carbonyl oxygen in variously substituted camphors would show a dependence on the $\langle r^{-3} \rangle_{2p}$ term which is associated with electron density on the oxygen, since other factors are unchanged. No such relationship is found and instead the ^{17}O shieldings (Table 4) remain the same throughout the series which embrances a wide range of electronic character of the substituent $X=H \rightarrow X=NO_2$.

TABLE 1

SUBSTITUENT PARAMETERS

X	En[26]	σ_I[a]	σ_I[b]	σ_I[c]	Es[27]
H	2.1	0	0	0	1.24
Me	2.3	0.02	-0.04	-0.01	0.00
Et		0.00	-0.03	-0.01	-0.07
NMe_2					
Ph	2.75	0.15	0.12		-2.48
$HC=CH_2$		0.08	0.09		-1.53
C≡CH		0.30	0.35		
OMe		0.34	0.29	0.32	
CHO	2.69				
OAc		0.41			
COOH	2.6			0.32	
Cl	3.25	0.48	0.47	0.50	
I	2.66	0.47	0.39	0.58	
CN	2.49	0.57	0.57	0.58	
NO_2	3.7	0.68	0.76	0.72	-1.28

a σ_I pkQui Table 10.4 Ref.27

b σ_I pkAc Table 10.4 Ref.27

c σ_I pkBCO Table 10.4 Ref.27

TABLE 2

^{13}C CHEMICAL SHIFTS (ppm.) OF 4-SUBSTITUTED CAMPHORS 13 - 25

X	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)
H	57.4	218.4	43.1	43.2	27.0	29.9	46.6	19.7	19.1	9.2
Et	59.7	218.6	46.1	48.4	31.2	29.3	49.6	17.6	16.0	9.85
Ph	60.9	217.1	47.0	53.1	32.2	29.3	50.6	18.0	16.75	10.1
$HC=CH_2$	59.7	217.0	45.9	52.1	31.8	29.4	49.2	17.7	16.3	9.8
NMe_2	59.1	215.7	43.0	70.0	28.1	26.3	48.8	18.8	17.8	9.7
C≡CH	58.1	215.3	48.1	43.5	33.8	29.1	50.25	18.0	16.7	10.0
OMe	57.9	214.6	44.8	84.3	29.2	27.9	48.4	17.3	15.55	9.7
CHO	60.2	215.0	42.6	60.6	29.2	28.1	51.3	18.2	17.7	8.9
OAc	56.45	212.8	46.0	84.0	30.0	28.6	48.7	17.2	15.6	9.6
I	54.0	213.8	54.6	45.0	40.0	30.2	51.6	19.0	18.4	10.3
CN	57.6	211.5	45.5	42.3	31.6	28.5	50.7	18.0	17.0	9.5
$CO\bar{N}\overset{+}{N}Me_3$	60.25	219.8	46.35	46.35	30.5	29.8	49.6	18.7	17.5	9.7
$CO\bar{N}\overset{+}{S}Me_2$	60.25	218.3	46.55	56.09	30.9	29.6	50.0	18.5	17.3	9.7

TABLE 3

^{13}C CHEMICAL SHIFT INCREMENTS (ppm.) OF 4-SUBSTITUTED CAMPHORS 13 - 25.

X	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)
H	0	0	0	0	0	0	0	0	0	0
Et	2.3	0.2	3	5.2	4.2	-0.6	3	-2.1	-3.1	0.65
Ph	3.5	-1.3	3.9	9.9	5.2	-0.6	4.0	-1.7	-2.35	0.9
$HC=CH_2$	2.3	-1.4	2.8	8.9	4.8	-0.5	2.6	-2.0	-2.8	0.6
NMe_2	1.7	-2.7	-0.1	26.8	1.1	-3.6	2.2	-0.9	-1.3	0.5
C≡CH	0.7	-3.1	5.0	0.3	6.8	-0.8	3.65	-1.7	-2.4	0.8
OMe	0.5	-3.8	1.7	41.1	2.2	-2.0	1.8	-2.4	-3.55	0.5
CHO	2.8	-3.4	-0.5	17.4	2.2	-1.8	4.7	-1.5	-1.4	-0.3
OAc	-0.95	-5.6	2.9	40.8	3.0	-1.3	2.1	-2.5	-3.5	0.4
I	-3.4	-4.6	11.5	1.8	13.0	0.3	5.0	-0.7	-0.7	1.1
CN	0.2	-6.9	2.4	-0.9	4.6	-1.4	4.1	-1.7	-2.1	0.3
$CO\overset{-}{N}\overset{+}{N}Me_3$	2.85	1.4	3.25	3.15	3.5	-0.1	3.0	-1.0	-1.6	0.5
$CO\overset{-}{N}\overset{+}{S}Me_2$	2.85	-0.1	3.45	12.9	3.9	-0.3	3.4	-1.2	-1.8	0.5

TABLE 4

^{17}O CHEMICAL SHIFTS (ppm*) OF 4-SUBSTITUTED CAMPHORS

Compound	^{17}O chemical shift
Camphor	520.3
4-chloro Camphor	520.9
4-nitro Camphor	520.9
4-iodo Camphor	519.0

* In ppm relative to external H_2O.

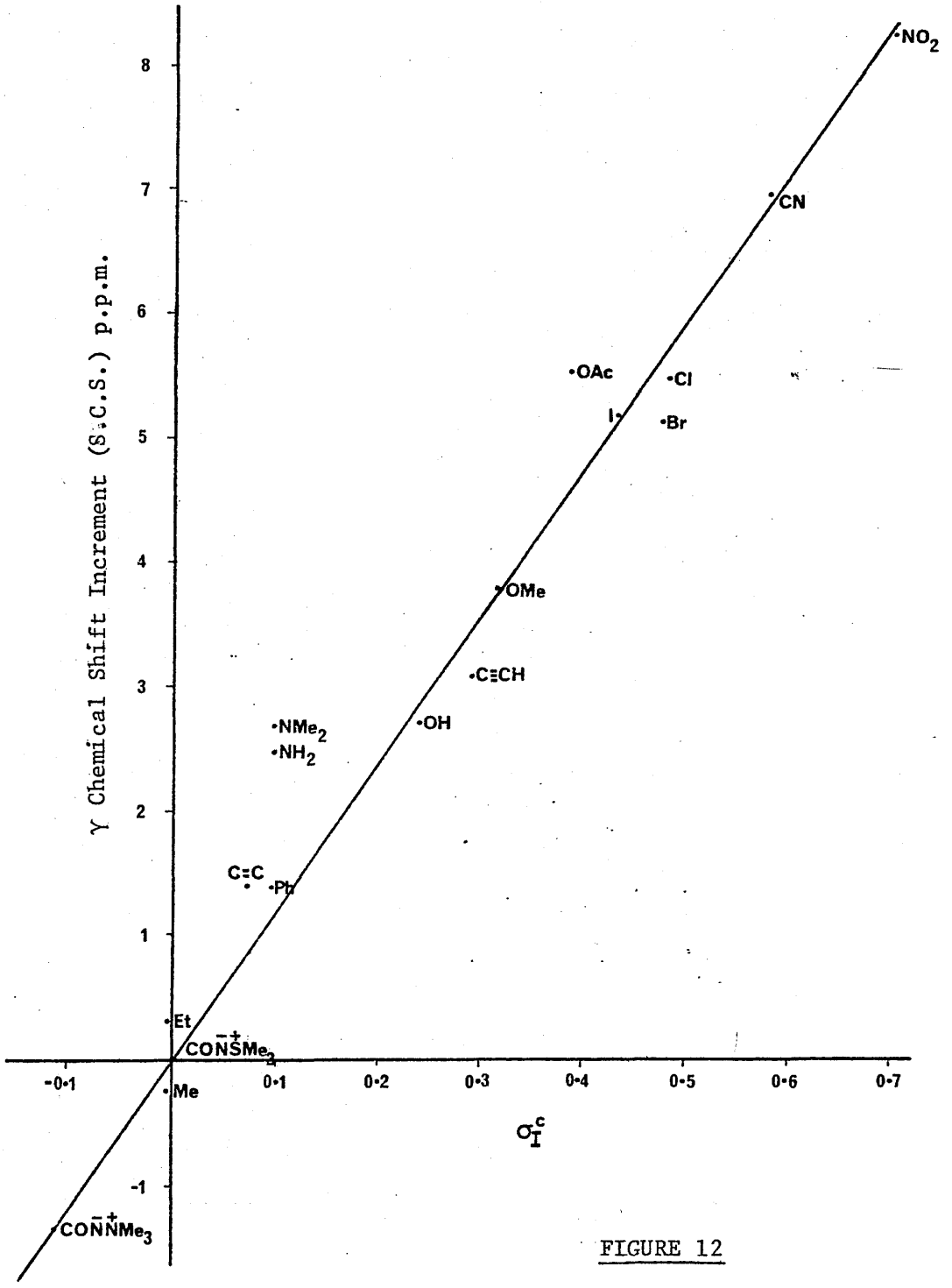


FIGURE 12

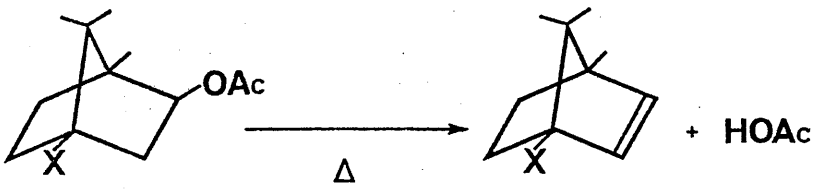
γ CHEMICAL SHIFT INCREMENT (ppm.)
OF 4-SUBSTITUTED CAMPHORS VERSUS σ_I^c

PART 2

THE GAS PHASE PYROLYSIS OF 4-SUBSTITUTED ISOBORNYL ACETATES

A large amount of research has been carried out on the topic of ester pyrolysis since its discovery more than a century ago. Although modern methods and techniques have aided in these inquiries, the subject still manages to elude total understanding, especially in the area of β-substituents. This study was primarily undertaken in order to examine the influence of C(4) substituents of isobornyl acetates on the rate of elimination, and secondly to ascertain whether rearrangement products arise from neighbouring group participation of the C(1) - C(6) bond which is known to occur in other reactions of the bornane system.

The pyrolysis of the 4-substituted isobornyl acetates 26 - 32 in the presence of a chain inhibitor, propene yielded a mixture of $C_{10}H_{15}X$ hydrocarbons, together with their derivatives and acetic acid. For a normal elimination as shown, Fig.13, the theoretical stoichiometry requires that the final pressure, Pf be twice the



X = H, CH_3, C_6H_5, OAc, Cl, CN, NO_2

Figure 13

initial pressure, Po. However, the average experimental results of Pf/Po after ten half lives and at four different temperatures were as follows: isobornyl acetate, 2.91; 4-methyl isobornyl acetate, 3.12; 4-phenyl isobornyl acetate, 3.03; 4-acetoxy isobornyl acetate, 3.31; 4-chloro isobornyl acetate, 2.33; 4-cyano isobornyl acetate, 2.72 and 4-nitro isobornyl acetate, 2.16. The higher value of Pf/Po is due to formation of other than the normal elimination products of substituted bornylene and its isomers. These were mainly substituted trimethylcyclopentadienes and ethylene formed by retro Diels-Alder reaction of the bornylene.

The homogeneous nature of the eliminations was examined by comparing the rate of pyrolysis in a packed vessel with surface-to-volume ratio of 6.14 times greater than the normal reaction vessel. For each ester decomposition, packing has no significant effect on the rate coefficient as long as the vessel is seasoned with allyl bromide.

The rate coefficients were determined by a titrimetric method, and the k values were found to be the same at different percentages of decomposition at each working temperature. The rate of elimination is independent of the initial pressure and the first order plots are linear up to 50% decomposition. The effect of temperature on the rate coefficients for elimination is given in Table 5. The results from this table give, by employing the least squares procedure and 0.8 confidence limits, the Arrhenius parameters shown in Table 6.

The percentage of each hydrocarbon formed in the pyrolysis of isobornyl acetate is given in Table 7. In order to evaluate whether rearrangement reactions were taking place, bornylene and its isomers, camphene and tricyclene were separately introduced into the reaction

vessel in the presence of acetic acid and propene inhibitor, conditions which simulate as closely as possible those of the pyrolysis experiment. The results obtained, are given in Table 8 and illustrate that the product distribution derived from bornylene isomerisation is very similar to that got from the pyrolysis of isobornyl acetate. As the temperature at which the isomerisation is carried out increases, the formation of camphene, tricyclene and trimethylcyclopentadienes becomes more favourable indicating the relative thermal stabilities of the various isomers and retra Diels-Alder products. Non-conversion of camphene into other products under pyrolysis conditions tends to support the idea that this isomer acts as the thermodynamic 'sink' for the reaction. The data given in Table 8 may imply that bornylene 53 is the primary product, while tricyclene 34 and camphene 54 are merely secondary isomerisation products, and that trimethylcyclopentadienes and ethylene are products of retro-Diels-Alder addition of bornylene. This scheme is represented in Fig. 14.

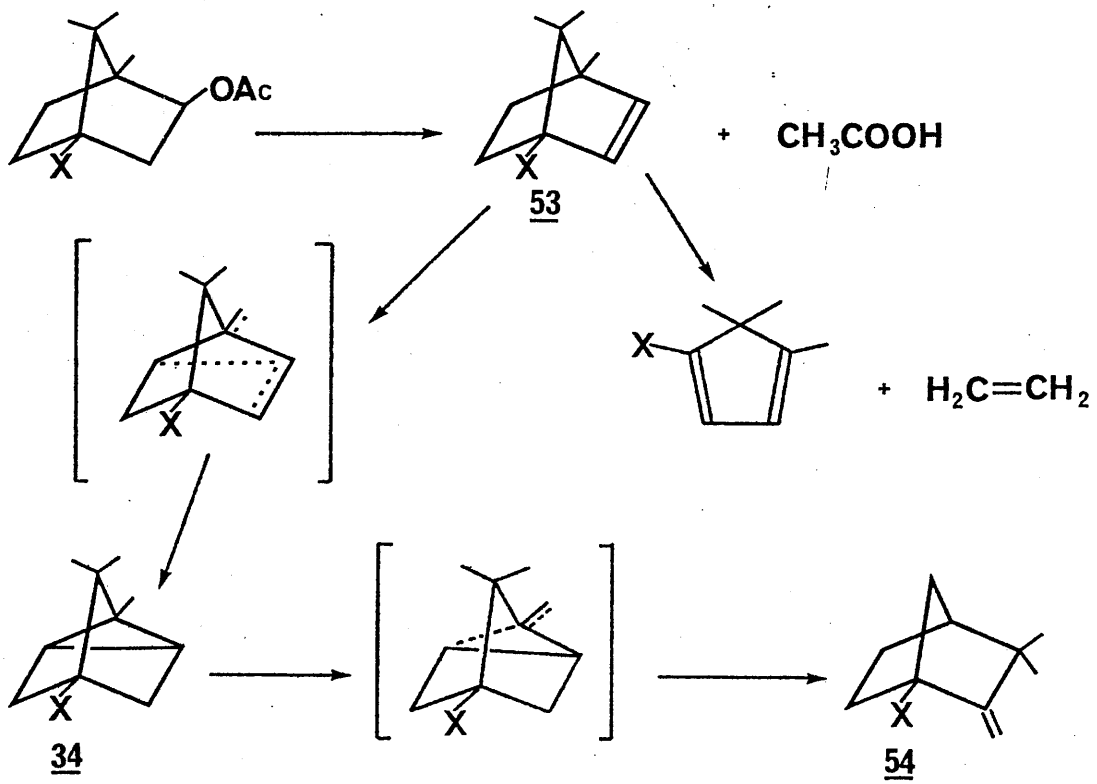


Figure 14

The relative reactivities for the gas-phase thermal decomposition of the 4-substituted isobornyl acetates are given in Table 6. These show that electron attracting substituents have a small deactivating effect upon the rate of elimination; a Hammett $\sigma\rho$ plot for the polar substituents OAc, Cl, CN and NO_2 yields a reasonable correlation, characterised by a gradient (ρ) of -0.689 and correlation coefficient of 0.926 (Fig. 15). Weakly inductive substituents, exemplified by methyl, show no such correlation and in fact accelerate the rate relative to that of the unsubstituted acetate. Despite the limited range of substituent studied, there appears to be a correlation between E_s, the linear free energy steric parameter and the rates of elimination for the aforementioned substituents. This phenomenon of steric acceleration has been noted in previous studies[135, 136] as being responsible for a marked rate increase.

It had been hoped that the pyrolysis of 4-substituted isobornyl acetates would yield informative and unambiguous kinetic data concerning the cyclic mechanism of the elmination process; it was assumed that a substituent effect study would reveal invaluable information regarding the charge accumulation in the transition state, or more accurately, the extent of movement of the electrons 1, 2 and 3 in Fig. 16.

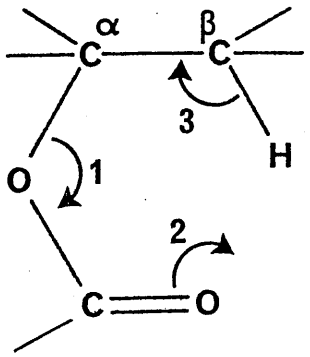


Figure 16.

Similar studies on arylethyl acetates by Taylor had uncovered much information pertaining to the extent of carbonium character located on the α carbon[121, 122] in the transition state for elimination.

Previous work had revealed that in a series of 4-substituted bornanones, electron-withdrawing substituents had a marked effect upon the base catalysed proton exchange rate;[208] the assumption was therefore made that if heterolysis of the C(3) - H(3exo) bond were critical in the rate-determining step (arrow 3 in Fig. 16) then the acidifying effect in, say for example, 4-nitro isobornyl acetate would result in that compound having a greater rate of elimination. The observed rates oppose this supposition and may substantiate the isotope effect studies repeated by Taylor[120] which indicated a transition state with little carbon-hydrogen bond breaking.

Difficulties have always existed when attempting to rationalise observed experimental facts in terms of reaction mechanisms; never more so than with acetate pyrolysis, where a six-membered ring transition state is proposed. Substituents sited so as to influence a particular reaction centre may in fact affect other atoms also involved in the transition state. Such primary and secondary effects of substituents are major reasons for the serious inconsistencies which exist in the accumulated data on ester pyrolysis. This conflict can clearly be seen in the present study; the primary effect is felt at the β-carbon, where bond rupture is aided by electron withdrawal; the secondary effect is upon the more remote α-carbon C(2) where the breaking of the C-O bond is facilitated by electron supply. The latter effect will be more pronounced for polar substituents due to the greater polarisibility of the C-O bond. The

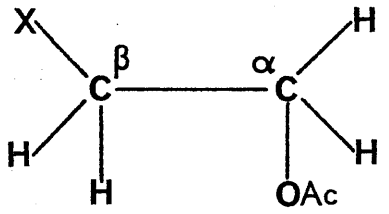
C(4) substituent in the isobornyl acetate may influence both α and β positions in opposing manner; results would indicate that the effect on the C(3) - H(3exo) bond cleavage is screened by a greater and contrary one at the α-carbon. Such a situation might arise if either the C-O bond rupture is far advanced of C-H bond cleavage in the transition state or the C(4) substituent is a powerful polar group.

In many previous studies,[209] ^{13}C chemical shifts have been taken as a measure of electron density on the carbon atom and employing this idea to the C(2) or α carbon of the present system reveals that electron density is greatest for the nitro substituted derivative and least for isobornyl acetate (see Table 9). If it is assumed that the change in electron density at C(2) (equivalent to a difference of 3.8 ppm. in the chemical shifts) is due entirely to the substituent at C(4), then perhaps a remote secondary substituent effect is in operation. The kinetic data for polar substituents can be explained in terms of either a secondary effect which swamps the primary effect at the β-carbon or a secondary effect with no primary effect due to non-participation of the C_β-H bond cleavage in the rate determining step. The latter explanation seems doubtful in the light of work carried out by Taylor,[120] which showed that C_β-H bond rupture had proceeded to at least a small extent in the transition state. The former explanation seems more probable since it considers a dominating rather than an exclusive effect acting on the α position. In a proposed semi-polar cyclic transition state, the α-carbon would become electron deficient (some carbonium ion character) and therefore

groups with the ability to donate electrons to the developing positive centre should stabilise the system and bring about rate enhancement. Conversely, destabilisation will result from an electron withdrawing group bonded to the α carbon. A large amount of experimental data supports this hypothesis. What type of mechanism might operate between C(2) and C(4) to account for the observed kinetics? As noted earlier, the high field shift of C(2) implies greater electron density on the carbon induced by the C(4) substituent; in a study on 4-substituted bornanones, it was observed that the C(2) carbonyl carbon chemical shift correlated well with the inductive power (σ_I) of the substituent.[200] This was accounted for by an inductive effect comprising of the normal through bond transmission and more importantly the field effect acting on the polarisable π electrons of the carbonyl. In that series, the chemical shift difference induced by the substituent was 8 ppm. between the nitro derivative and the unsubstituted compound which compares with 3.8 ppm. between the same two substituents in the present study; this variation in the shielding of the C(2) carbon in the two series may be due to the greater polarisability of the π electrons of a carbonyl moiety compared to the σ electrons of a C-O linkage. Since the only change that occurs on going from isobornyl acetate to the 4-nitro substituted acetate is the exchange of bridgehead substituent, it implies that the excess electron density which seems to be present on the carbon atom of the nitro derivative must be derived from the only polar bond directly attached to that atom, the C-O bond. In the bornanone series, it was found that increased electron density on the carbonyl carbon was accompanied by an increase in the infrared stretching

frequency[210] of the carbonyl which was attributed to a depolarisation of the bond with attendant bond shortening and strengthening. If an analogous bond order increase accompanied the observed electron density increase for polar substituents in the acetate series, then this might explain the experimental results; greater bond strength in the C-O linkage would result in a slowing down of the rate, assuming that C-O bond cleavage is crucial in the transition state. Past studies have indicated the importance of this bond rupture in the reaction mechanism.[121, 122]

Other studies of β-substituents,[126, 135, 136] carried out, primarily on substituted ethyl acetates 55, have revealed similar rate retardations with polar groups such as OMe and Cl. However,



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unlike the present investigation in which the substituent is situated so as to produce primarily inductive effects, the former studies have employed systems which allow other polar and steric contributions to operate. For example, the methoxy group, as well as having an inductive (-I) effect, also possesses a large mesomeric (+M) effect on account of the oxygen lone pair, which can function in the above situation. It has been postulated that the observed rate reduction

for the methoxy derviative results from the mesomeric effect opposing and dominating the inductive contribution (Fig.17). This argument is somewhat controversial, since it has been pointed

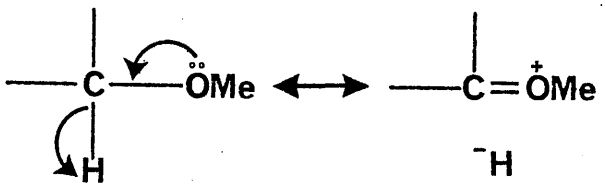


Figure 17

out that a +M effect (electron donating) is not likely to play an important role at a centre (β-carbon) where at least some negative charge is developing.[136] Secondly, if, as Taylor has said, C-H bond cleavage has not progressed far in the transition state, then such a factor would have minimal effect on the rate.

In an effort to measure purely the inductive effect of a β-substituent, a series of propyl acetates was studied[135] in which the polar substituent was insulated from the β-carbon by a methylene group. In the absence of the rate retarding mesomeric (+M) effect, the rate increased quite considerably for substituents which had originally shown retardation in the ethyl acetate series. In the same study, 3-acetylpropyl acetate was pyrolysed and the rate of elimination was found to be only 3.14 times faster than ethyl acetate as compared to a factor of 240 between 2-acetylethyl acetate and ethyl acetate. This dramatic reduction in reactivity was attributed to

the cancellation of a mesomeric (-M) effect by the intervening

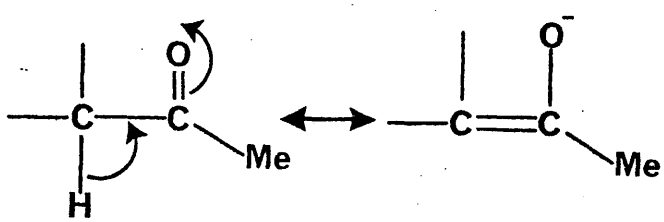


Figure 18

methylene group, which had contributed favourably toward the rate of elimination (Fig. 18). These results were interpreted as providing evidence of an acceleration of the rate of elimination by solely inductive effects originating from a β-substituent. In the absence of other effects, particularly mesomeric ones, it follows that as the inductive power of the substituent increases so should the rate. However, if mesomeric influences are present (as in the 2-substituted ethyl acetates), the rate is a function of both types of electronic effect; rate retardation relative to ethyl acetate occurring if mesomeric factors dominate and enhancement if the opposite situation occurs. Such a hypothesis initially appears valid since it accounts for much of the experimental data; however more detailed examination reveals certain anomolies which exist in the literature and do not conform to the above treatment. Pyrolysis of 2(dimethylamino) ethyl acetate is faster than the methoxy derivative;[136] NMe_2 has a very large mesomeric effect and a smaller

inductive effect than methoxy and should be expected to produce a slower rate of elimination. Likewise, the fluoro-derivative has a rate[136] which is approximately the same as that for methoxy, but according to the proposed hypothesis it should be far faster, since it has a large -I effect and small +M effect.

Other work that has been cited as evidence of rate enhancement by β-polar substituents is that of Bailey and King[211] who found that pyrolysis of 1-methyl, 2-nitro ethyl acetate gave only 1-nitro prop-1-ene.

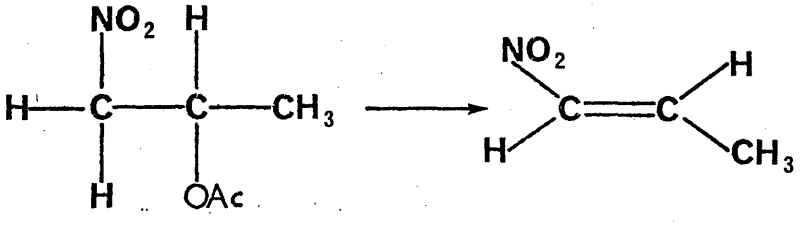


Figure 19

Since it is possible for elimination to occur in one of two ways, the isolation of only one product was accounted for by the enhanced reactivity in the eliminated acetate induced by the nitro group (Fig.19). However, the above experiment was not a kinetic study and therefore the product obtained is perhaps the most thermodynamically stable, produced by a rearrangement after the elimination. A second factor which should be mentioned regarding this evidence, is that the nitro moiety like cyano and acetyl possesses a mesomeric (-M) effect which would almost certainly operate producing an extremely acidic β-proton favouring elimination.

So far, little mention has been made of steric acceleration in the discussion. It is unanimously accepted that steric acceleration is present when β-alkylation occurs and this arises from the fact that in the transition state the hybridisation at both α and β carbon atoms changes from sp^3 to sp^2 resulting in the relief of strain which will exist between substituents on these carbon atoms. Rate enhancement produced by steric factors in acetate pyrolysis is small in comparison with the changes in the rate attributable to other factors.[135, 136] It seems reasonable, then, to assume that steric acceleration will only be observed and consequently be of any importance when other effects are absent or negligible. In the present study, although steric factors are probably in operation throughout the series (since all the substituents produce greater steric strain than a proton), it is only where the inductive effect is very small that steric acceleration is observed; the geometry of the bicyclic system, however, minimises the contribution which derives from these steric influences. The same cannot be said for the study on propyl acetates; the rate changes observed between substituted propyl acetates and similarly substituted ethyl acetates were accounted for by the elimination of either a retarding +M effect or an accelerating -M effect, leaving purely an accelerating inductive effect. In comparison with the bicyclic series, the lack of rigidity in this system will allow a larger contribution from steric factors which may play an important part in the observed rates, especially when it is remembered that the inductive effect falls off by 2.3 per intervening carbon atom. Similarly, the proposed rate enhancement brought about by the nitro group in the pyrolysis of 1-methyl,

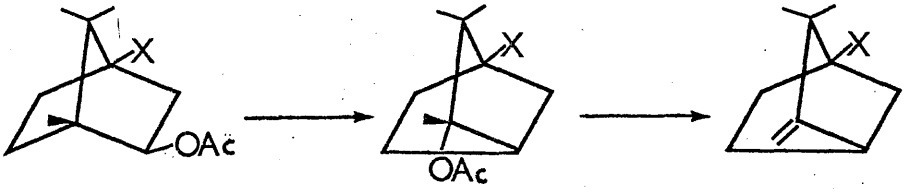
2-nitro ethyl acetate would be supplemented by steric acceleration produced by the methyl group attached to the adjacent carbon.

From the foregoing discussion, it is clear that the experimental data pertaining to the influence of β-polar substituents on the kinetics of acetate pyrolysis is indecisive with results obtained from various studies often contradicting one another; theories put forward may account for some of the inconsistencies, but by no means are they universal.

A major objection to accepting the suggestion that the present rate data referring to the polar substituted isobornyl acetates is attributable to a remote inductive/field effect acting between C(2) and C(4) is that such an effect, if it existed, would have to be large enough to be 'felt' at that distance and at the same time counteract the β-carbon effect. A recent study[200] on the sodium borohydride reduction of a series of 4-substituted bornanones has revealed a large rate increase associated with electron withdrawing substituents such as nitro which gives a rate enhancement of 30 relative to unsubstituted ketone. Although the reduction is obviously more sensitive and susceptible to substituents ($\rho \simeq 2$) than the present reaction, the results do at least show that a long range inductive effect could be operating; allied to this, is the ^{13}C N.M.R. of the acetates which show a definite change in the electronic environment of C(2) due, almost certainly, to a change in substituent. A plot of σ_I of the substituent against the chemical shift difference (S.C.S.) yields an approximate correlation (Fig.20). These two facts give more credibility to the long-range inductive theory, especially if the

β-carbon-hydrogen bond breaking is insignificant in the transition state.

It has been suggested that a rearrangement of the acetates may take place prior to elimination, resulting in substituted esters whose pyrolysis kinetics are in accord with previous studies. The known propensity of related systems to Wagner-Meerwein and other rearrangements is considered adequate evidence to suggest such a process might occur. The proposed rearrangement has been envisaged as shown in Fig.21, where synartetic assistance by the electrons of the 1,6



56

Figure 21

bond leads to the rearranged ester 56, which is ca 40 times more reactive than the initial acetate.[212] Similar 1,2 migrations have been noted for xanthates, where the sulphur atom is more nucleophilic and hence more disposed to a rearrangement as shown in Fig.22.

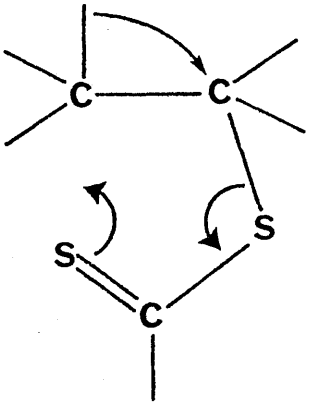


Figure 22

However, the proposed rearrangement for the present series of acetates, if it indeed occurs, must proceed via a carbonium ion or radical intermediate since the bicyclic geometry militates against a concerted process. Similarly, the strained ring structure must invalidate the concerted double retention isomerisation mechanism envisaged by Taylor and reported in a recent review.[212]

Pyrolysis of the rearranged ester 56 would yield camphene and tricyclene (Fig.23); recalling that the stability of the three $C_{10}H_{15}X$ isomers decreases along the series camphene > tricyclene > bornylene, then no bornylene or its retro Diels-Alder addition products, trimethylcyclopentadienes and ethylene, could be formed in this particular pyrolysis. Since the pyrolysis of isobornyl acetate produces moderate amounts of the latter compounds it seems reasonable to suppose that an alternative reaction must be responsible for their existence. It is

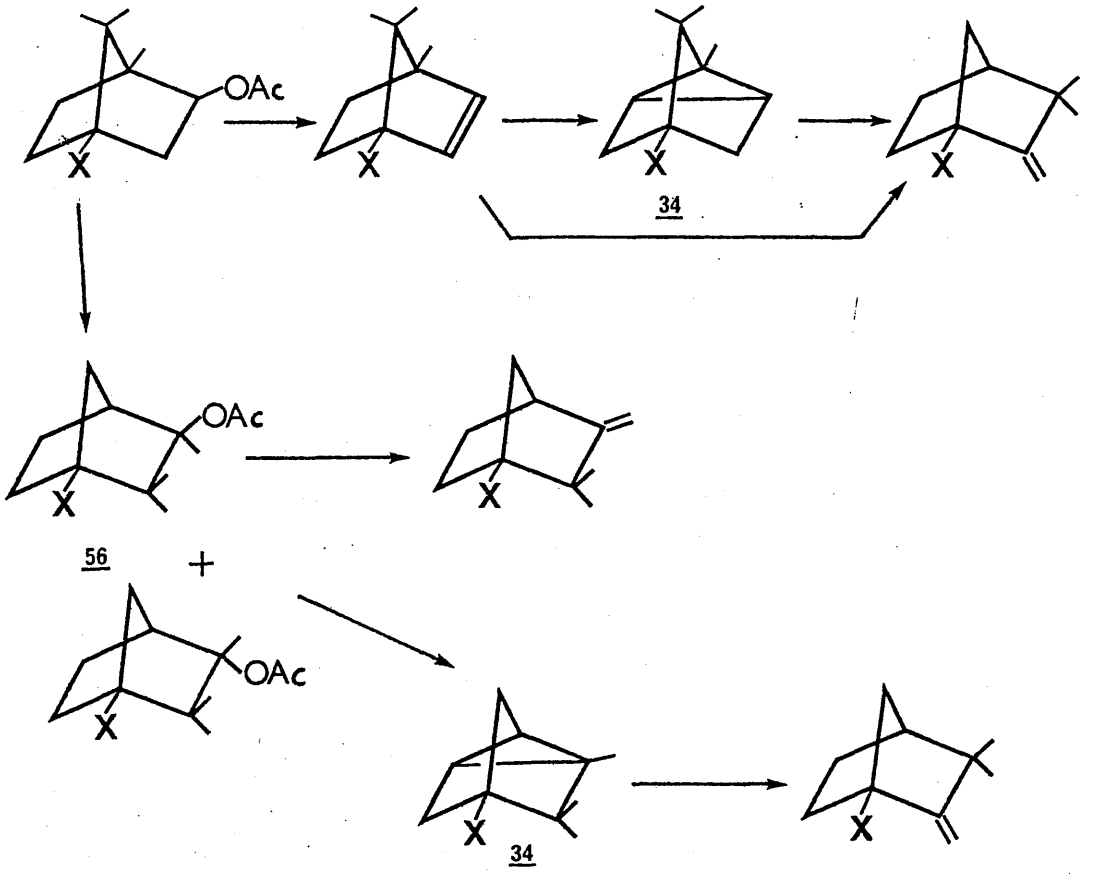


Figure 23

apparent from Figure 23 that if pyrolysis of the rearranged acetate 56 were occurring to any great extent, the product distribution obtained would be quite different from the distribution which is found when bornylene is isomerised under pyrolysis conditions; camphene and tricyclene would be formed preferentially, but no such build-up of these compounds is noted in the pyrolysis of isobornyl acetate. This suggests that the postulated rearrangement is either of minor importance or does not occur at all. The existence of a carbonium ion on the α-carbon in ester pyrolysis (in the form of an ion-pair) was disproved several years ago,[131] so the possibility of a rearrangement occurring via a carbonium ion intermediate seems somewhat dubious despite the known ease of the bicyclic system to undergo intramolecular rearrangements. The proposed formation of tricyclene 34 via a 1,3 elimination[250] of 56 as shown in Figure 23, is an example of the propensity of the system to yield rearranged products; the elimination would almost certainly proceed by a concerted process which is more credible than the rearrangement proposed by Taylor,[212] since now the bicyclic geometry is no longer opposed to the requirements of a synchronous process.

Although the pyrolysis of the rearranged acetate 56 would lead to substituent effects in accord with other studies[121,126] on α-substituents, namely, that electron withdrawing groups retard the rate and weak electron releasing groups accelerate the elimination, presumably by the same steric effects proposed for C_β substituents, it seems that the kinetics obtained are explained more fully in terms of a direct elimination prior to rearrangement.

TABLE 5

THE EFFECT OF TEMPERATURE ON THE RATE COEFFICIENT k_1

COMPOUND								
26	TEMPERATURE (^{o}C)	321.8	329.2	340.5	344.1	350.0	359.4	368.9
	$10^4 k_1$ (sec^{-1})	1.58	2.53	5.07	6.30	8.92	15.36	26.19
28	TEMPERATURE (^{o}C)	310.2	319.1	328.8	340.1	344.2	350.0	359.5	370.0
	$10^4 k_1$ (sec^{-1})	1.01	1.80	3.31	6.59	8.47	11.79	20.27	36.21
27	TEMPERATURE (^{o}C)	289.8	300.1	310.2	319.9	332.3	344.1		
	$10^4 k_1$ (sec^{-1})	0.53	1.06	2.05	3.78	8.05	16.08		
31	TEMPERATURE (^{o}C)	310.0	320.9	325.1	329.8	341.1			
	$10^4 k_1$ (sec^{-1})	0.48	0.99	1.30	1.75	3.53			
30	TEMPERATURE (^{o}C)	325.9	330.0	339.1	344.1	349.3	359.5	370.3
	$10^4 k_1$ (sec^{-1})	1.45	1.86	3.30	4.60	6.21	10.85	20.85
32	TEMPERATURE (^{o}C)	336.4	344.2	350.3	360.1	369.7		
	$10^4 k_1$ (sec^{-1})	1.43	2.29	3.33	5.92	10.21		
29	TEMPERATURE (^{o}C)	318.6	329.1	339.8	344.1	350.0	359.5	
	$10^4 k_1$ (sec^{-1})	0.45	0.88	1.73	2.25	3.20	5.57	

TABLE 6

KINETIC PARAMETERS FOR 4-SUBSTITUTED ISOBORNYL ACETATES PYROLYSES AT 340°C.

Substituent	$10^4 k_1$ (sec^{-1})	Relative rate	E_a (kJ mol^{-1})	log A (sec^{-1})	log k_{rel}
4-H	5.01	1.00	189.2(±1.5)	12.82(±0.13)	0.000
4-CH_3	6.50	1.30	186.7(±1.3)	12.72(±0.12)	0.113
4-C_6H_5	12.76	2.55	181.5(±1.6)	12.57(±0.15)	0.406
4-CH_3CO	3.35	0.69	190.9(±3.8)	12.79(±0.34)	-0.175
4-Cl	3.53	0.71	191.8(±2.1)	12.89(±0.18)	-0.162
4-CN	1.78	0.36	192.6(±0.9)	12.66(±0.08)	-0.450
4-NO_2	1.75	0.35	191.5(±1.2)	12.56(±0.11)	-0.457

TABLE 7

YIELD OF PRODUCTS FROM ISOBORNYL ACETATE PYROLYSIS[a] AT SEVERAL TEMPERATURES.

Product	Temperature, °C		
	320	340	370
Bornylene	22.3	23.6	24.8
Tricyclene	14.8	12.2	9.4
Camphene	50.1	52.8	55.4
Trimethylcyclopentadienes	12.7	11.8	11.2

[a] Ethylene is obtained in about the same proportion of the trimethylcyclopentadienes.

TABLE 8

PRODUCT DISTRIBUTION OF THE BICYCLIC $C_{10}H_{16}$ COMPOUNDS.

	Temperature (°C)	Bornylene	Tricyclene	Camphene	Trimethylcyclo-pentadienes
Bornylene	340	24.4	8.6	48.8	17.3[a]
	370	21.2	9.1	49.1	20.0[a]
Tricyclene	340	-	93.5	6.2	-
	370	-	92.4	7.4	-
Camphene	340	-	99.7	-	-
	370	-	99.3	-	-

[a] Ethylene is formed in the same proportion.

TABLE 9

^{13}C CHEMICAL SHIFTS (ppm.) OF 4-SUBSTITUTED ISOBORNYL ACETATES 26 - 33, 72

X	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)†	C(9)†	C(10)
H	48.60	80.76	38.79	45.10	27.09	33.80	46.91	19.90	20.14	11.37
Me	50.52*	79.88	45.56	47.78*	33.25	34.43	46.86*	17.66	17.72	12.16
Ph	51.82*	79.63	43.63	54.53*	32.62	33.01	50.44*	18.35	18.57	12.35
Cl	49.72*	77.82	46.84	72.74	36.06	32.28	47.28*	17.44	17.53	12.72
OAc	48.22*	78.10	40.34	86.84	29.71	32.10	45.53*	17.43	17.61	11.90
CN	51.67*	77.84	42.47	43.92	31.83✓	32.39✓	49.84*	18.18	18.48	11.57
NO_2	51.63*	76.91	41.50	93.22	31.14✓	31.33✓	50.05*	17.68	18.05	11.92
I	51.07*	79.15	50.75	43.47	39.90	34.26	49.60*	19.28	19.28	12.64
C≡CH	50.76*	79.03	44.73	45.16	27.09	33.99	49.55*	18.11	18.36	12.01

Acetate ^{13}C absorptions are between 169.70 - 170.42 ppm. for the ten acetate carbonyls and the corresponding methyl groups absorb between 20.91 - 21.16 ppm. Additionally, the substituent at C(4) absorbs at the following positions in the compounds itemised: 4-CH_3, 15.69; 4-CN, 120.86; 4-Ph, 140.87, 127.83, 127.34, 126.08; 4 C≡CH, 85.44 and 70.4 ppm.

Assignments indicated by *, † or ✓ may be reversed.

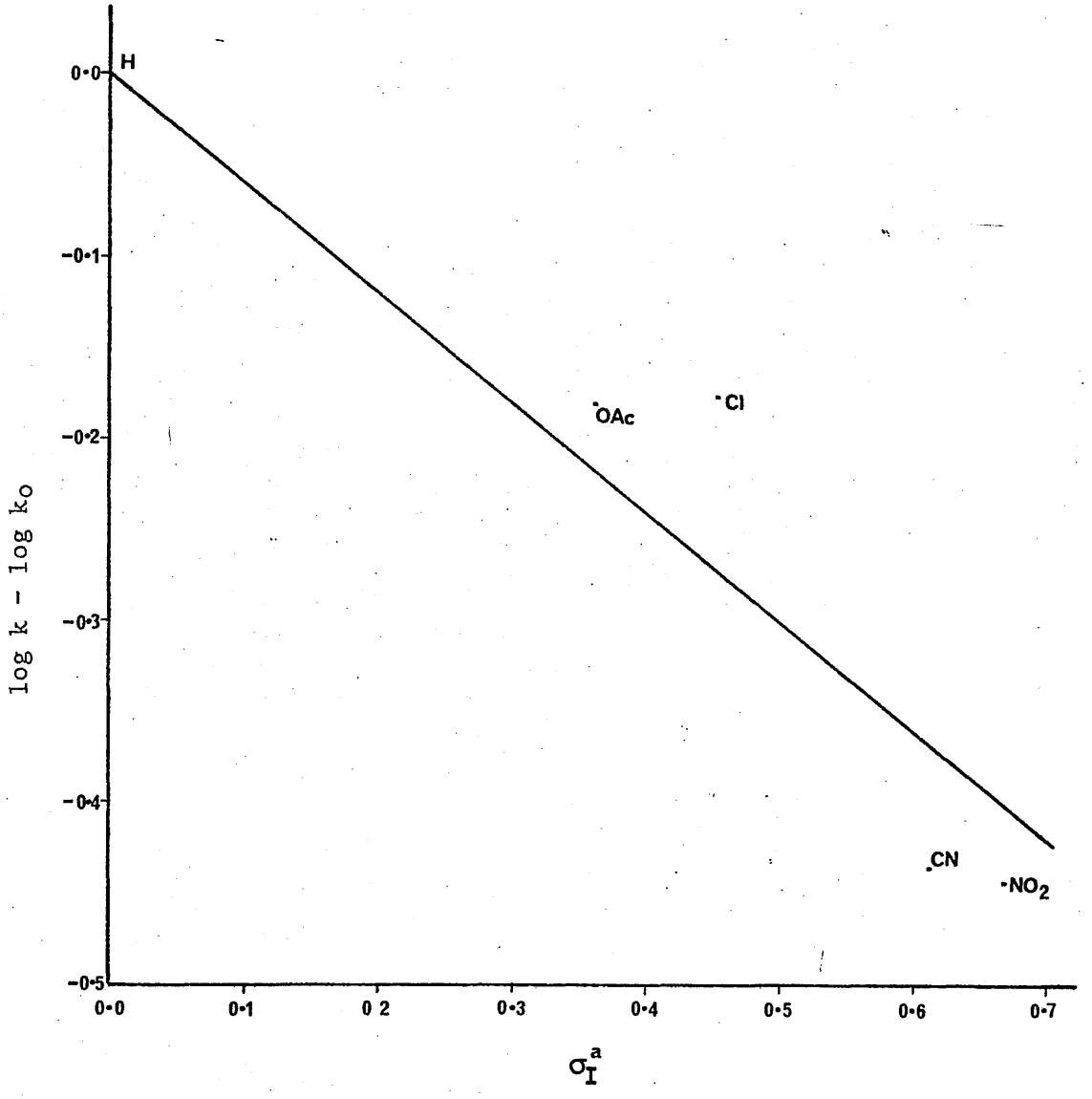


FIGURE 15

LOG k - LOG k_o FOR THE PYROLYSIS OF 4-SUBSTITUTED ISOBORNYL ACETATES VERSUS σ_I^a.

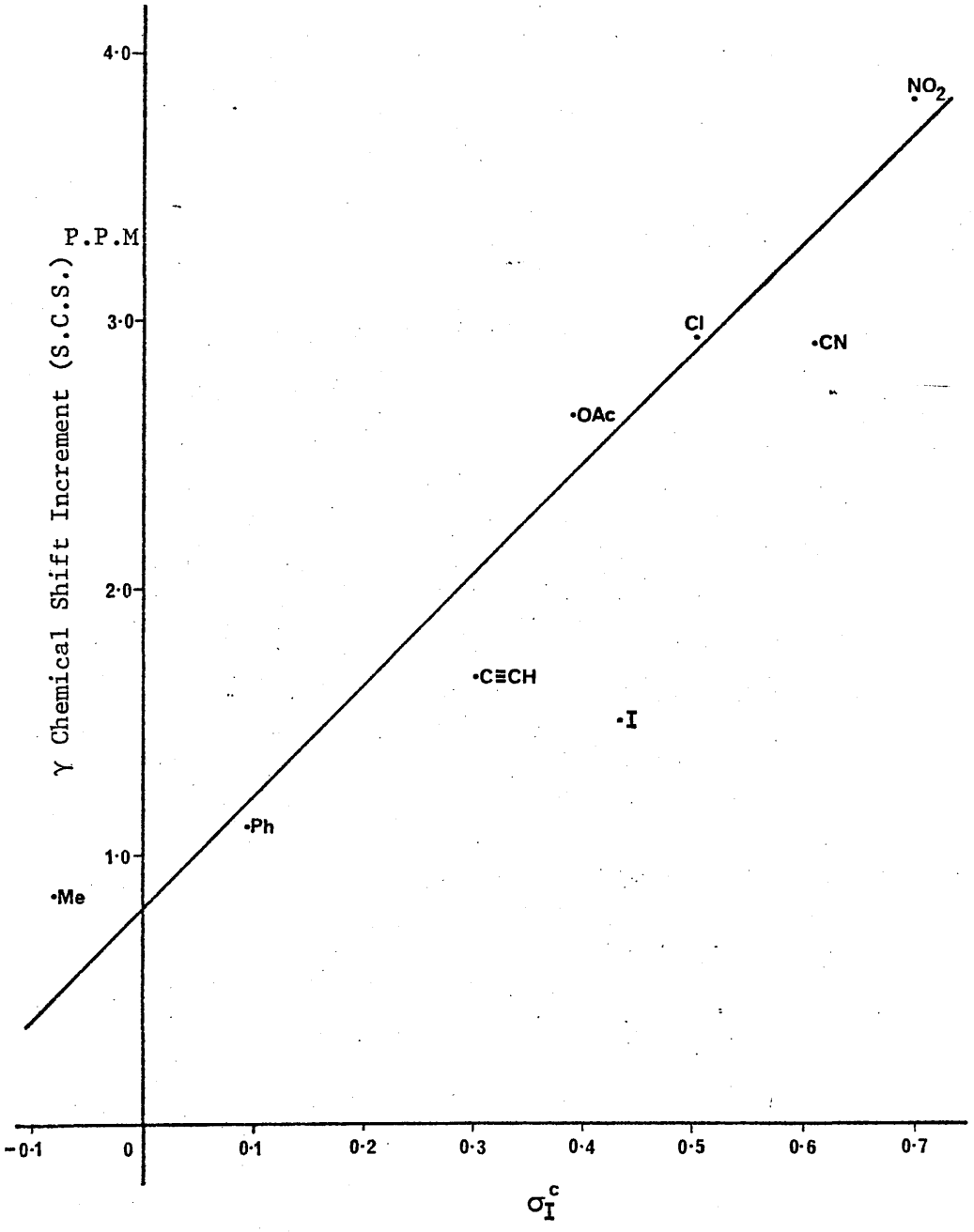


FIGURE 20

γ CHEMICAL SHIFT INCREMENTS (P.P.M.) OF 4-SUBSTITUTED ISOBORNYL ACETATES VERSUS σ_I^c.

PART 3

SODIUM BOROHYDRIDE REDUCTION OF 4-SUBSTITUTED BORNANONES

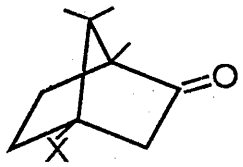
Apart from its obvious use in preparative organic chemistry, sodium borohydride has become an important reagent for investigating the reactivity of aldehydes and ketones toward nucleophilic addition. Through the work of Brown and others, a great deal of information has accrued, concerning this versatile and stable reducing agent and its mode of reduction. Although the stoichiometry and kinetics of the process have been known for several years, a detailed understanding of the mechanism involved, including transition state geometry at the rate determining step is lacking. The present work was undertaken in an attempt to clarify some of the mechanistic ambiguities which have been discovered by previous substituent effect studies and kinetic isotope effect studies.

The rates of reduction of a series of 4-substituted bornanones by sodium borohydride were studied and the observed substituent effects considered mechanistically.

The choice of C(4) as the site for the substituent is not an arbitrary one; situated at the bridgehead position the substituent is sufficiently distant from the reaction centre (C(2)) so as not to generate steric effects upon the rate but to produce, hopefully, purely inductive/field influences, transmitted through the σ and π bond framework and space respectively. Evidence to substantiate the validity of the proposal that the inductive effect originating from a C(4) substituent is the dominant contribution 'felt' at the C(2) carbon,

comes from studies which employed bridgehead-substituted fused ring systems for the investigation of ^{13}C chemical shift substituent effects. In particular, in a series of 4-substituted bornanones,[190] analogous to those employed in the current investigation, the C(2) carbon shifts displayed a reasonable correlation with the linear free energy parameter, σ_I, which is a measure of the inductive power of the substituent.

Despite experimental difficulties and preparative problems, eleven compounds were studied, encompassing as large a range of σ_I values as possible in order to produce a meaningful correlation.



	16 X = C_6H_5	
43 X = H	22 X = OCH_3	19 X = CN
35 X = CH_3	13 X = C≡CH	38 X = NO_2
18 X = $N(CH_3)_2$	37 X = COOH	36 X = Cl

The kinetics of the reduction were studied at 25.5°C in a solvent system comprising of 0.5 ml 0.1N NaOH, 0.5 ml H_2O and 2 ml dioxan and monitored by U.V. spectrometry. Results obtained are given in Table 10. Also tabulated are the ^{13}C chemical shifts of the C(2) carbon of each substituted compound and their shift difference relative to the unsubstituted bornanone.

In agreement with previous investigations[155,156] the reaction obeys second order kinetics and is clearly accelerated by electron-withdrawing groups.

The rate of reaction is determined by the initial slow hydride transfer from boron to carbon and the formation of an oxygen-boron bond as shown (Fig.24).

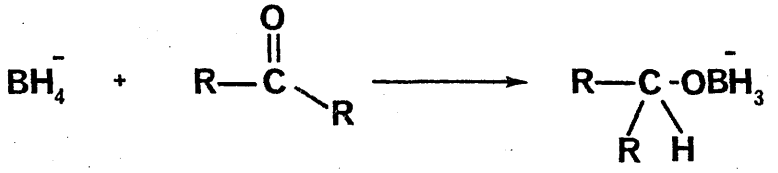


Figure 24

Bowden[157] and others have considered this transformation as occurring, in one of two ways; either by mechanism a) which involves a direct reaction pathway or mechanism b) which proceeds by the formation of a complex, followed by internal hydride transfer.

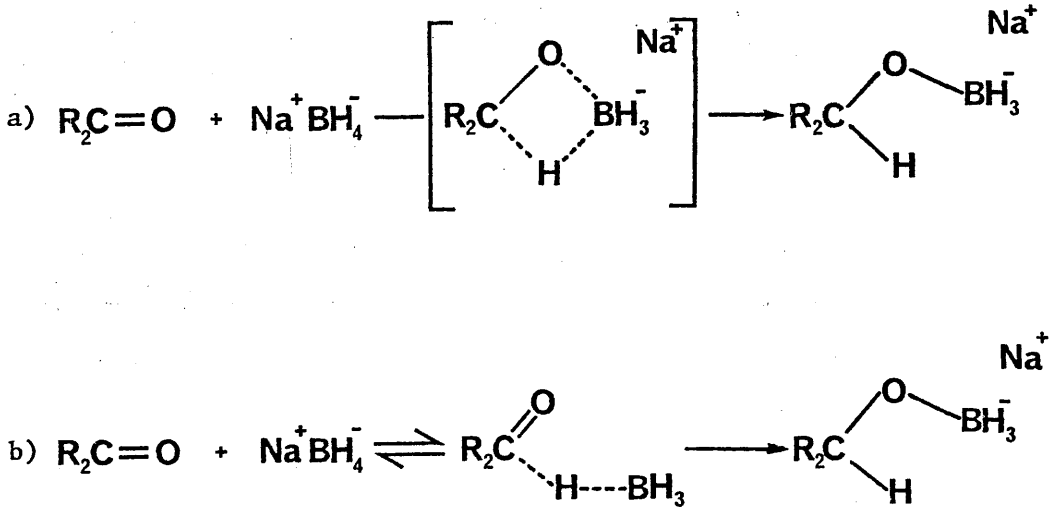


Figure 25

The concerted process described in a) implies a four-membered ring transition state incorporating a penta-coordinated boron anion and although such a species may exist when considering the reaction of borane with unsaturated compounds, the present situation is not comparable.[164] The step-wise mechanism as illustrated in b) is one of two possible sequences; either initial hydride transfer as shown or coordination of the tetrahydridoborate anion to the carbonyl moiety prior to hydride transfer. The former scheme would necessitate the production of borane while the latter would involve the formation of a penta-coordinated boron anion analogous to mechanism a).

Invoking Hammett's concept of $\sigma\rho$ relationships yields a large amount of data regarding the mechanism of the reaction (see Figures 26, 27 and 28). The correlations obtained using σ_I values derived from various sources are good with correlation coefficients of 0.980, 0.995 and 0.995. Not unexpectedly, the average reaction constant value ρ is +ve and has a magnitude of 2.07. Since ρ is a measure of the sensitivity of the reaction to substituent change and its sign indicates the electronic environment at the reacting centre relative to the initial state, these experimental results highlight certain aspects of the reduction mechanism. Firstly, contrasting the reaction constant obtained in the current investigation with those derived from earlier work on acetophenones[157] and fluorenones[155,156] yields a discrepancy in the magnitude of the constant. Several factors are probably responsible for the diminution of ρ in the present study, but dominant among these will be the difference in location of the substituent from the reaction site, in the various systems; earlier surveys employed perturbing groups in closer proximity to the carbonyl function while this investigation

relies on an effect transmitted from a source two carbon atoms distant. Assuming that any effect 'felt' at C(2) is due to an inductive factor, which is known to fall off by a factor of ca 2.3 per carbon atom, then the observed reduction of ρ in this system is in accord with the postulate of a pure inductive/field effect; the fact that the reaction constant is still as large as 2, indicates that despite a remote substituent effect, this type of reaction is highly sensitive to electron distribution. Common to all the studies carried out on the sodium borohydride reduction of carbonyl groups is the positive sign of the reaction constant which signifies that the transition state has a reaction centre which is electron rich relative to the initial state.

Several authors[151,155,157] have noted that the kinetics and Hammett analysis of borohydride reductions bear a close resemblance to those obtained for alkaline ester hydrolysis; investigations into this reaction have found ρ values ranging from 2.1 to 2.8 at 25 to 30°C in various solvents. The mechanisms for saponification involving bimolecular kinetics and acyl-oxygen cleavage ($B_{AC}2$) has been studied extensively by Bender,[213] who found by means of a labelling experiment, that the tetrahedral species X had a finite lifetime and was therefore an intermediate as opposed to a transition state (Fig.29). An analogous labelling experiment employing tritiated sodium borohydride as the marker and benzaldehyde as the carbonyl moiety confirmed the existence of an intermediate and a reversible step in the mechanism of reduction (Fig. 30).

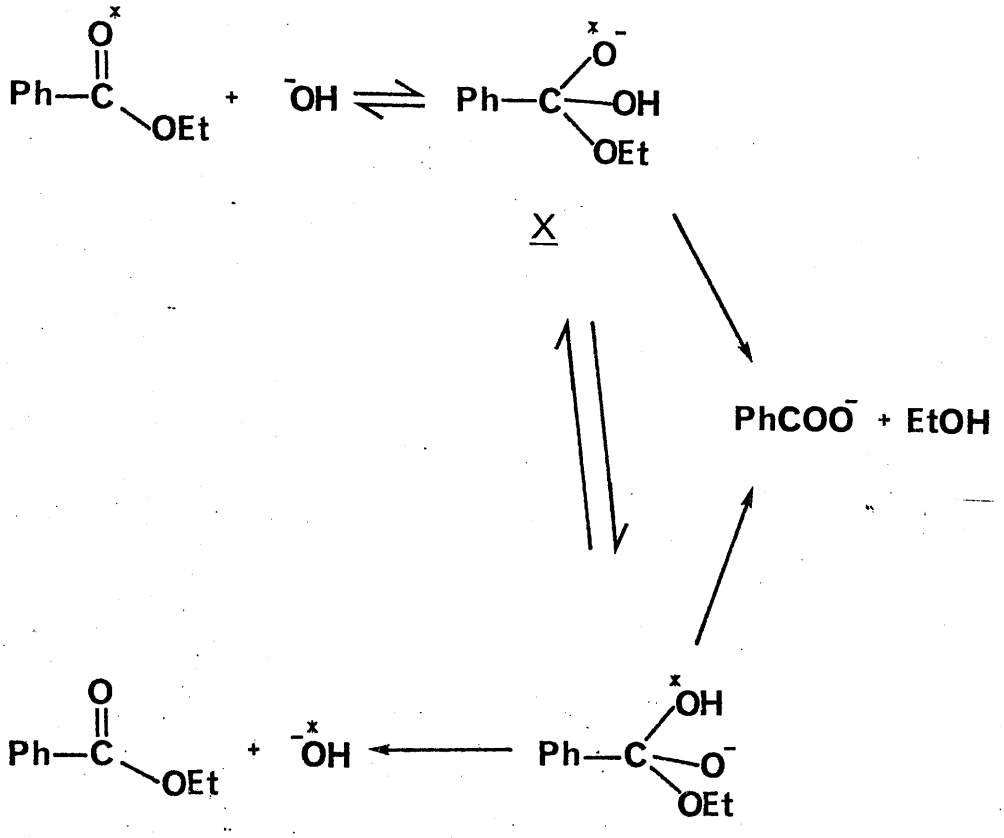


Figure 29

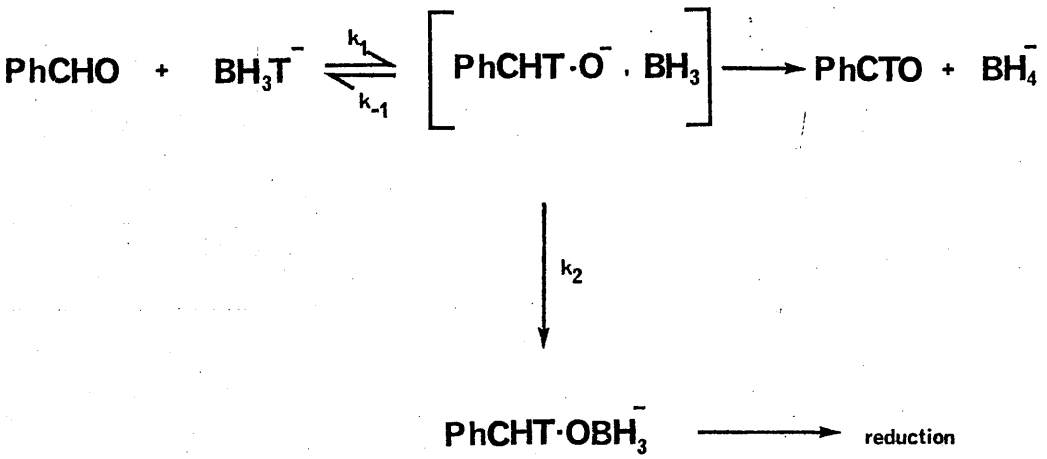


Figure 30

The authors considered the intermediate to be in the form of a caged pair, since reversibility of the hydride transfer after formation of the stable oxygen-boron bond was thermodynamically unfavourable.[164]

Besides the correlations obtained between log k_2 rel and σ_I (determined by various methods - pKQui, pKAc, pKBCO -) which are plotted on Figs. 26, 27 and 28, a reasonable linear relationship, ($r = 0.965$) is obtained when log k_2 rel is plotted against $\delta_H - \delta_X$, the difference in the chemical shift of the C(2) carbon of the carbonyl in the parent and substituted compound (Fig.31). The previously noted correlation[190] between σ_I and $\delta_H - \delta_X$ in the same system supports the existence of the present relationship. It is apparent that there exists an inter-relationship between the ^{13}C chemical shift of the carbonyl carbon, the reactivity of the carbonyl group toward reduction and the inductive power of a group substituted at the C(4) position of the bicyclic system. A detailed discussion of the three inter-related functions may now be made. The Hammett analysis of inductive effects due to a C(4) substituent and the corresponding ^{13}C chemical shift of the C(2) carbon was previously interpreted[190] in terms of the electron density about that carbon being directly related to the inductive effect produced. Although this survey has since been extended[200] to cover more electron releasing groups such as ylids ($C(O)\bar{N}\overset{+}{N}Me_3$, $C(O)\bar{N}\overset{+}{S}Me_2$), the initial investigation dealt with a σ_I range of approximately 0.7 which corresponded to a chemical shift difference of 8 ppm. Analysis of the results revealed that electron withdrawing

groups, such as nitro and chloro, shielded the C(2) carbon relative to the similar carbon in the unsubstituted bornanone. This was rationalised in terms of the redistribution of the electrons in the system creating greater shielding; proof of this rationale came from an infrared study of the carbonyl stretching frequencies in the same compounds.[104] It was observed that a rise in the carbonyl frequency ν_{CO}, resulted from electron withdrawing groups being substituted at the C(4) position. It is known that substituents with strong -I effects decrease the formal charge on the oxygen atom, by exerting a 'pull' on its electrons, with the effect that the polarity of the carbonyl bond is reduced; this in turn shortens the bond length and gives rise to the observed higher stretching frequency. Similar bond order changes have been found in other bicyclic systems, particularly substituted camphenilones[10] and bornan-2,3-diones.[210] From the above hypothesis, it is apparent then, that the positive character of the carbonyl carbon should decrease on going from X = H to X = NO_2, assuming that the only substituent effect in operation is the inductive/field effect. The consequence of this trend is to produce a reactivity series in contradiction to the experimental results, both in this study and previous ones, which unanimously agree that electron-withdrawing groups accelerate the rate; if the rate-determining step in the reaction were the initial nucleophilic attack of the hydride species on the carbonyl carbon then the aforementioned groups would deactivate the ground state resulting in a retardation of the rate relative to the unsubstituted substrate. Undoubtedly, the ^{13}C chemical shift

assigned to C(2) is the result of two opposing inductive effects; the first of these, and in this system, the more dominant of the two, is the depolarisation of the carbonyl bond; the second effect is the 'normal' through bond transmission which results in an attenuating charge alternation pattern as proposed by Pople.[57] (Fig.32).

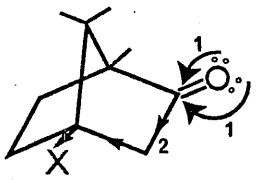


Figure 32

It is not surprising that the first effect is dominant, since the carbonyl group can be polarised (or depolarised) more readily than a methylene moiety. Comparing C(2) with the other γ carbon in the system, C(6), reveals that, as expected, substituent chemical shift (S.C.S.) values are more pronounced for the sp^2 hybridised carbon and correlate better with σ_I. A factor which has already been mentioned with regard to the magnitude of the reaction constant ρ, is the proximity of the substituent to the carbonyl function. Choice of the site closer to the reaction centre than in the present system may increase the contribution of the through bond mechanism to the overall inductive effect; however, it is more than likely that by doing so, other substituent effects will come into

operation. Brown has shown in a series of α-phenylacetones[148] that steric effects play an important role in the rate of reduction; similarly, mesomeric effects have been cited as the cause of the slower reaction times of acetophenone and benzophenone compared with acetone. A problem which arises when considering substituent effects is the difficulty involved in attempting to separate the various factors which contribute to the total effect of the substituent; these may be divided into steric and polar contributions, with a further sub-division of the polar effect into field (or direct), inductive (through bond polarisation involving σ or π electrons) and mesomeric effects. In practice, distinction between field and through bond effects is difficult and these are grouped together under the term inductive. It is quite probable that correlations involving substituent effect parameters would be found more often if the different contributions, mentioned above, for a given substituent reinforced one another. This is rarely the case, however, and as an example, the methoxy group has an -I effect with an opposing +M effect. To circumvent this problem, many studies have been carried out employing <u>meta</u> and <u>para</u> substituted benzene rings[157] as the perturber group so as to avoid opposing electronic effects. The study of α-phenyl acetones,[148] is a good example of polar and steric contributions counteracting one another. In the present investigation, the reasonable correlation recorded, employing variously determined σ_I values lends support to the hypothesis that a C(4) substituent should only give rise to an inductive effect; several substituents have opposing electronic contributions which would result in a large discrepancy in the correlation were mesomeric effects being transmitted.

The current study differs significantly from past surveys of the borohydride reduction. Firstly, a system has been employed which isolates the carbonyl moiety from any substituent effect, other than inductive; 4-substituted cyclohexanones[149,150] which were also used in a polar effect study exhibited some conformational effects, which are absent in the rigid bicyclic framework of bornanone. Secondly, the electronic structure, particularly at the reaction centre C(2) in the ground state is better understood due to ^{13}C N.M.R.

The analogy between the mechanism of borohydride reduction and that of alkaline ester hydrolysis ($B_{AC}2$) has previously been made; esters and amides, in general, already possess a carbonyl carbon which is electron rich in comparison with aldehydes and ketones as indicated by the higher field shift of the former in the ^{13}C N.M.R. spectrum, attributed primarily to a mesomeric effect. It would be expected then, that electron-withdrawing groups will further deactivate the group toward nucleophilic attack. However, in a similar manner to that observed for reduction, electron attracting substituents enhance the rate of hydrolysis.

To account for the obvious difficulties which are present in an interpretation of the data obtained from ^{13}C and kinetic studies (this work) a closer examination of the rate determining step and its geometry must be made. Recent evidence,[164] regarding the mechanism has revealed that a reversible hydride transfer takes place which will allow for the possibility of a certain amount of thermodynamic control to exist in the reduction process. If it is assumed that the transient intermediate formed is as Gold has postulated, then such a species would be stabilised by electron withdrawing groups as would the subsequent adduct. The observed

rate constant, k_{obs}, would be a product of the equilibrium constant K and k_2, the rate constant for the formation of the adduct:-

$$k_{obs} = Kk_2$$

Recalling that the positive character of the carbonyl carbon is diminished by electron withdrawing groups, then k_1, which is a measure of the rate of nucleophilic attack at the carbonyl, will be smaller for these substituents. In order to obtain kinetics in accord with experimental results, the equilibrium constant K must be significant. (Fig.33). If the intermediate is

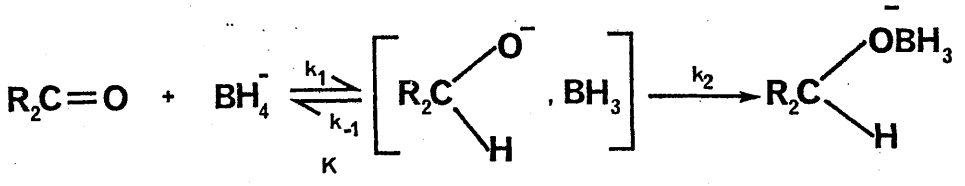


Figure 33

stabilised in the presence of electron-attracting substituents, K will be large and rate enhancing; where little stabilisation occurs (electron releasing groups or substituents with low σ_I values) K may be small and rate retarding.

From the above rationale, it appears that the proposed equilibrium (hydride transfer) greatly influences the kinetics

observed and the attendant substituent effects. It is known that

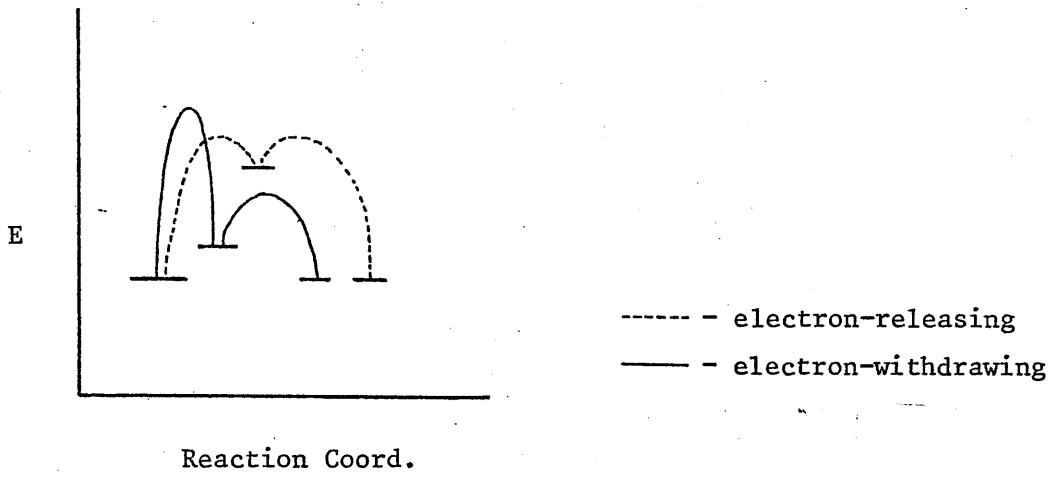


Figure 34

aqueous acid hydrolysis of benzamides[214] involves a multistep process including an equilibrium, which is dependent upon the strength of the acid used. (Fig. 35). In dilute acid, the equilibrium lies

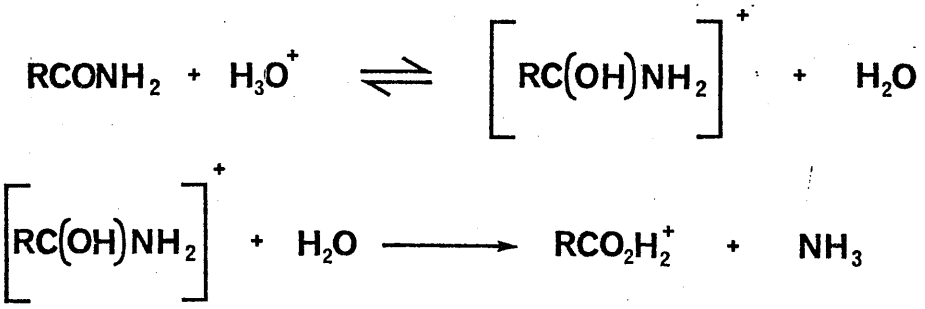


Figure 35

to the left, and it is found that the reaction is almost independent of polar effects since these would have opposite effects in the two steps.

However, in strong acid the equilibrium is complete and the large polar effects observed are due entirely to those operating in the second step. It is postulated that similar equilibrium control exists in borohydride reduction but unlike the above example where acid strength controls the position of the equilibrium, the stability of the intermediate is the dominant factor.

$$K = \frac{\left[R_2C(H)-O\cdots BH_3\right]}{\left[R_2C{=}O\right]\left[BH_4^-\right]}$$

Figure 36

This study corroborates that done by Gold et al[164] who discovered the existence of a reversible step in the reduction process; in the absence of an equilibrium, the unambiguous polar effects observed would contradict other postulated second order mechanisms.

TABLE 10

RATE CONSTANTS ($1.mole^{-1}sec^{-1}$) FOR SODIUM BOROHYDRIDE REDUCTION OF 4-SUBSTITUTED BORNANONES IN DIOXAN : H_2O AT 25.5°C.

X	λmax nm	εc=o	$k_2 x 10^5 m^{-1} s^{-1}$	k_2 rel	log k_2 rel	^{13}C Chemical Shift of C(2)	^{13}C Chemical Shift Increment
H	287	30	2.75	1	0	218.4	0.00
CH_3	285	39	2.95	1.07	0.03	218.7	-0.30
NMe_2	285	34	5.10	1.85	0.27	215.71	2.69
Ph	286	36	6.10	2.22	0.35	217.08	1.32
OMe	286	31	9.02	3.28	0.52	214.65	3.35
C≡CH	286	32	13.9	5.05	0.70	215.26	3.14
COOH	287	33	15.9	5.39	0.73	215.7	2.70
Cl	287	27	23.4	8.51	0.93	212.85	5.55
CN	286	26	72.5	26.36	1.42	211.47	6.93
NO_2	282*	88*	87.3	31.75	1.50	210.01	8.39

* λmax ketone = 282 nm (ε = 88)
λmax alcohol = 280 nm (ε = 69)

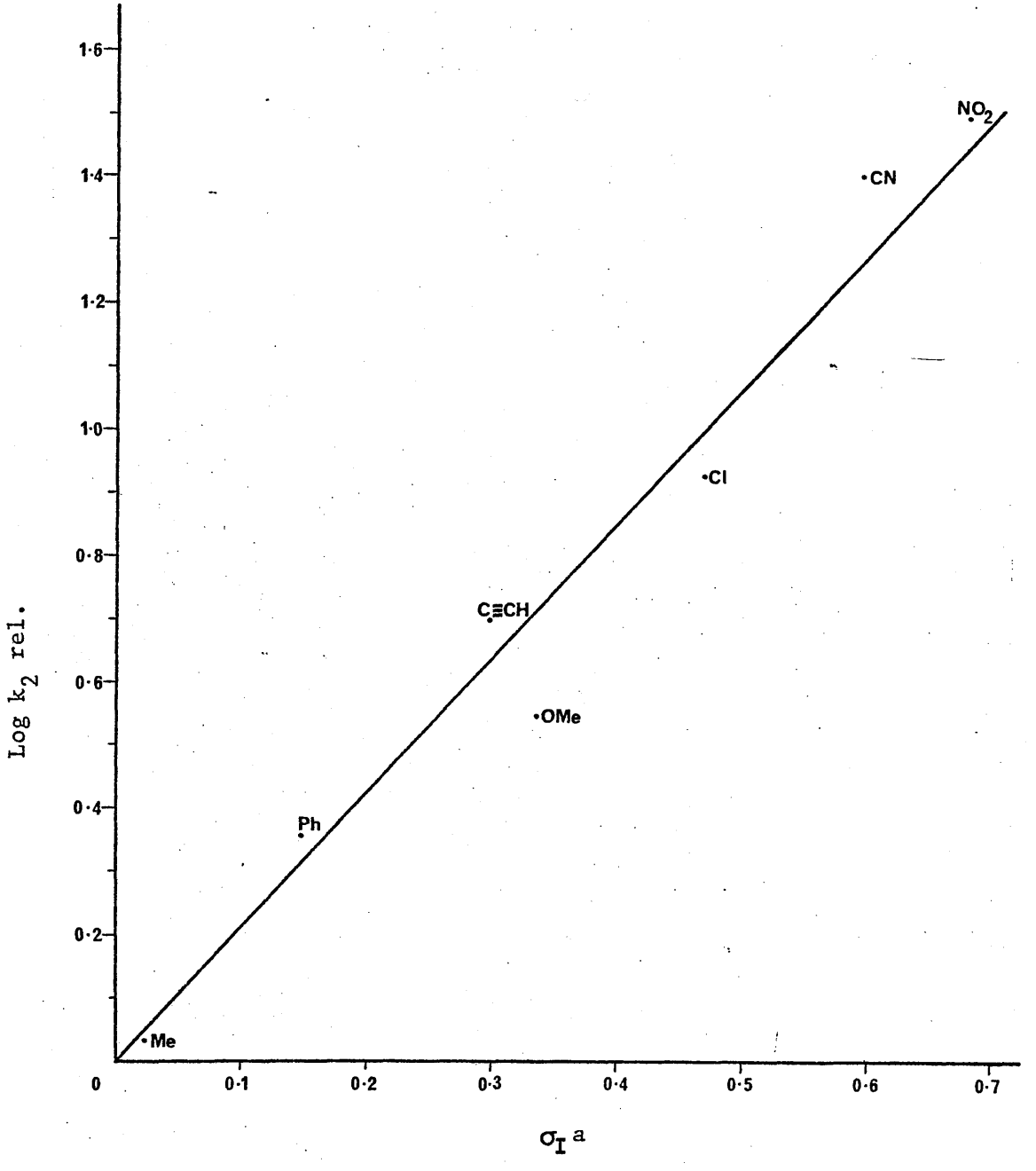


FIGURE 26

LOG k_2 rel FOR THE REDUCTION OF 4-SUBSTITUTED BORNANONES VERSUS $\sigma_I{}^a$.

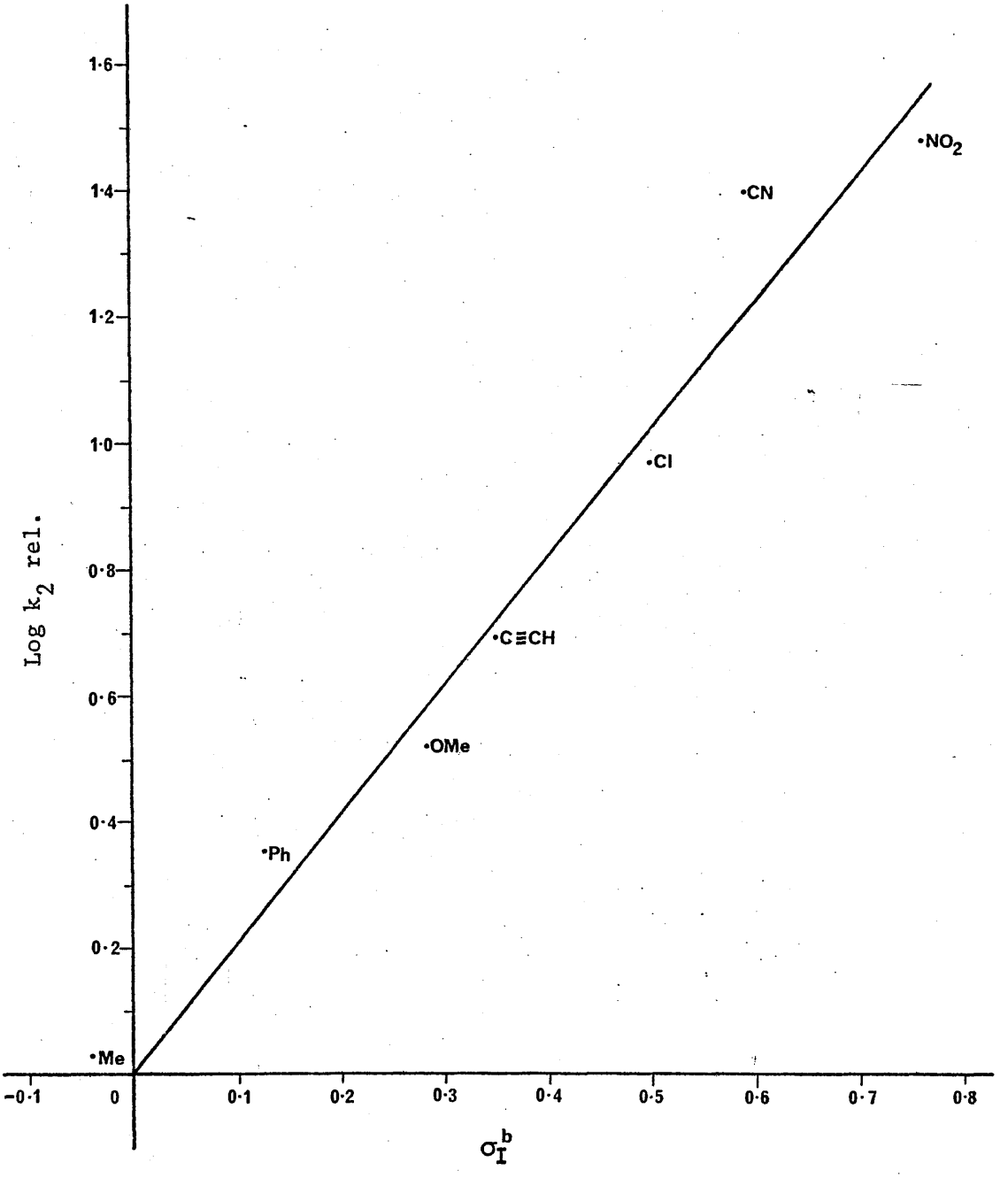


FIGURE 27

LOG k_2 rel FOR REDUCTION OF 4-SUBSTITUTED BORNANONES VERSUS σ_I^b.

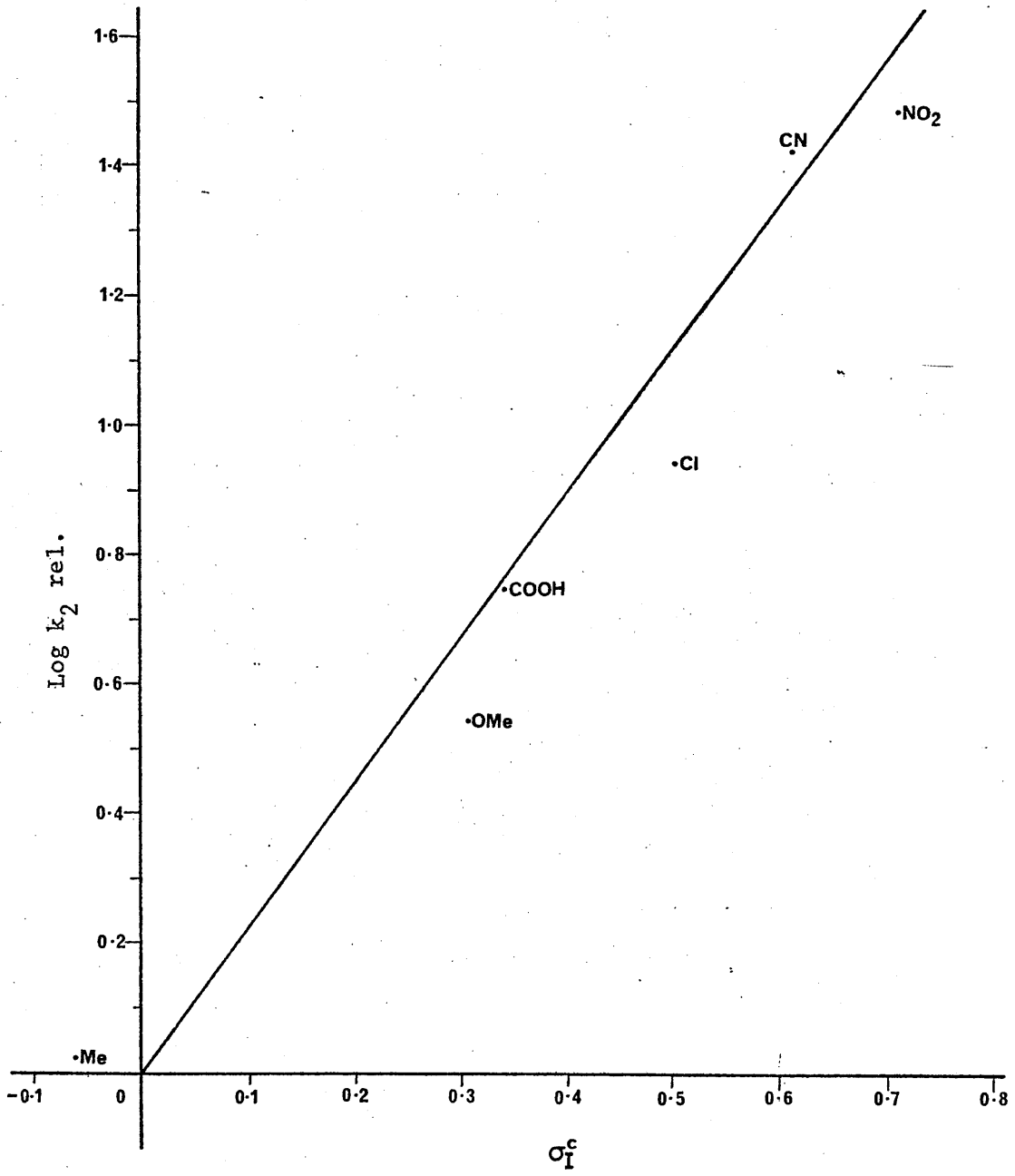


FIGURE 28

LOG k_2 rel FOR THE REDUCTION OF 4-SUBSTITUTED BORNANONES VERSUS σ_I^c.

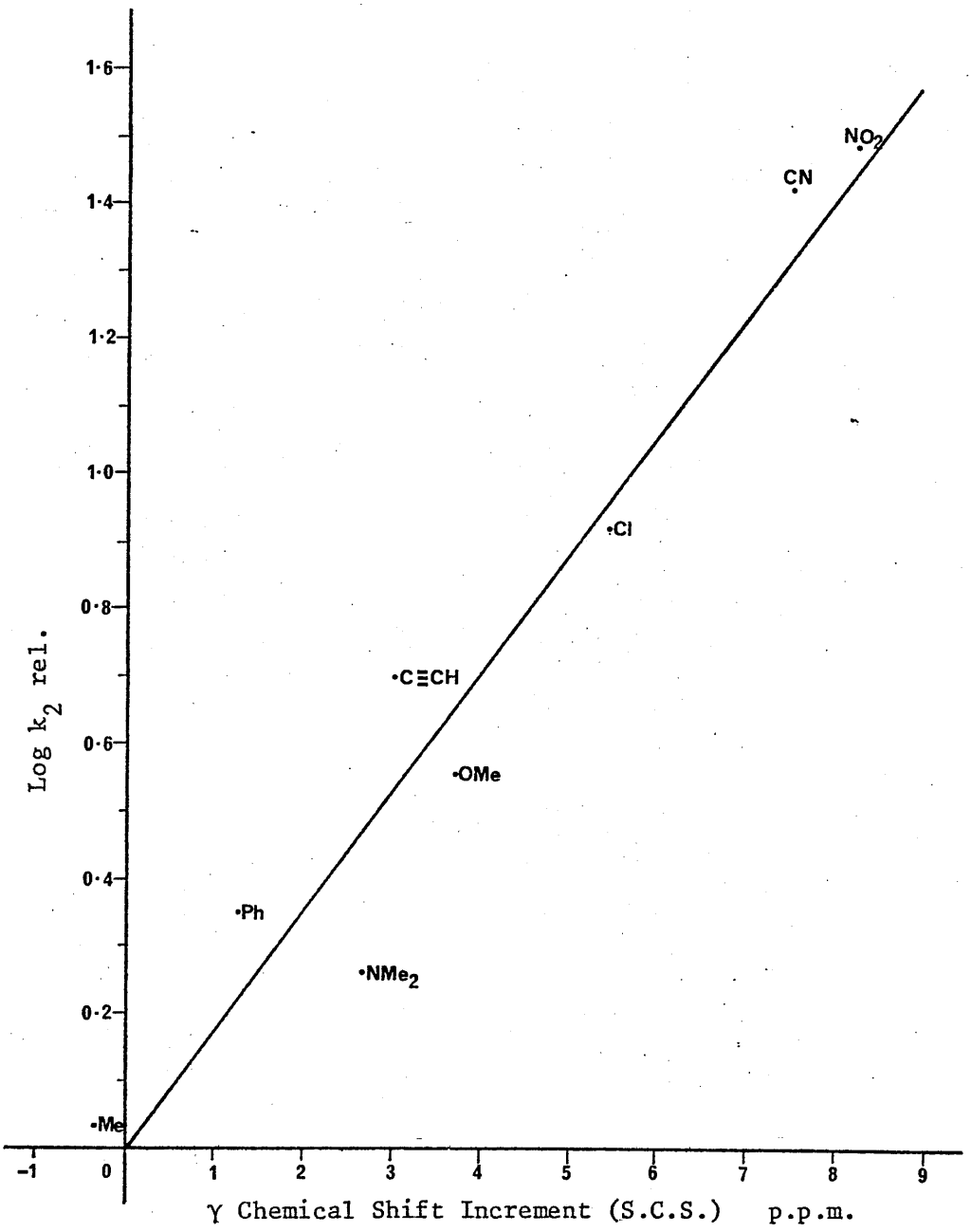


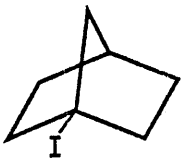
FIGURE 31

LOG k_2 rel FOR THE REDUCTION OF 4-SUBSTITUTED BORNANONES VERSUS THEIR γ CHEMICAL SHIFT INCREMENT (p.p.m.)

MISCELLANEOUS EXPERIMENTS

PHOTOLYSIS REACTIONS OF IODO-BORNANE DERIVATIVES

During the attempted synthesis of 4-methoxy camphor 22, one unsuccessful route pursued was analogous to that followed by Poindexter and Kropp[215] in their preparation of 1-methoxy and 1-ethoxy norbornanes. This involved the photolysis of the iodo-derivative in the appropriate solvent, namely ethanol, for the synthesis of the ethyl ether and methanol for the methyl ether; yields of greater than 60% were obtained for both norbornane ethers. On the basis that the two systems, bornanes and norbornanes, possessed similar geometries, it was decided to carry out an analogous photochemical reaction to produce the corresponding methoxy bornane derivative. However, in contrast to 1-iodo norbornane 57, the iodine containing compounds, suggested as precursors (1-iodo camphene 58 and 4-iodo camphor 20), possessed functionality other than a bridgehead iodine and a hydrocarbon skeleton allowing for the possibility of more complex photobehaviour.



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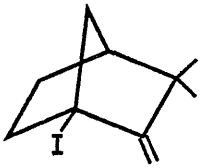

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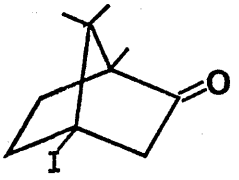


20

The photochemistry of alkyl halides has been extensively studied,[216, 217] but not until recently was it shown that electron

transfer between the initially generated radical pair could occur affording an ion pair.[215] In consequence, both radical and carbocationic products are possible, as shown in Figure 37.

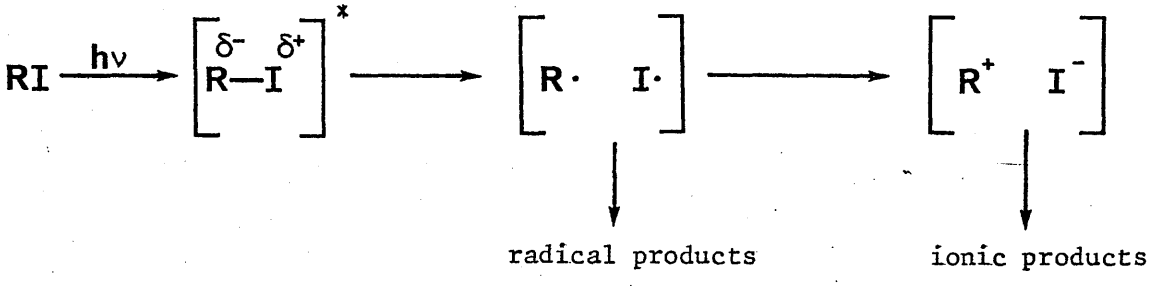


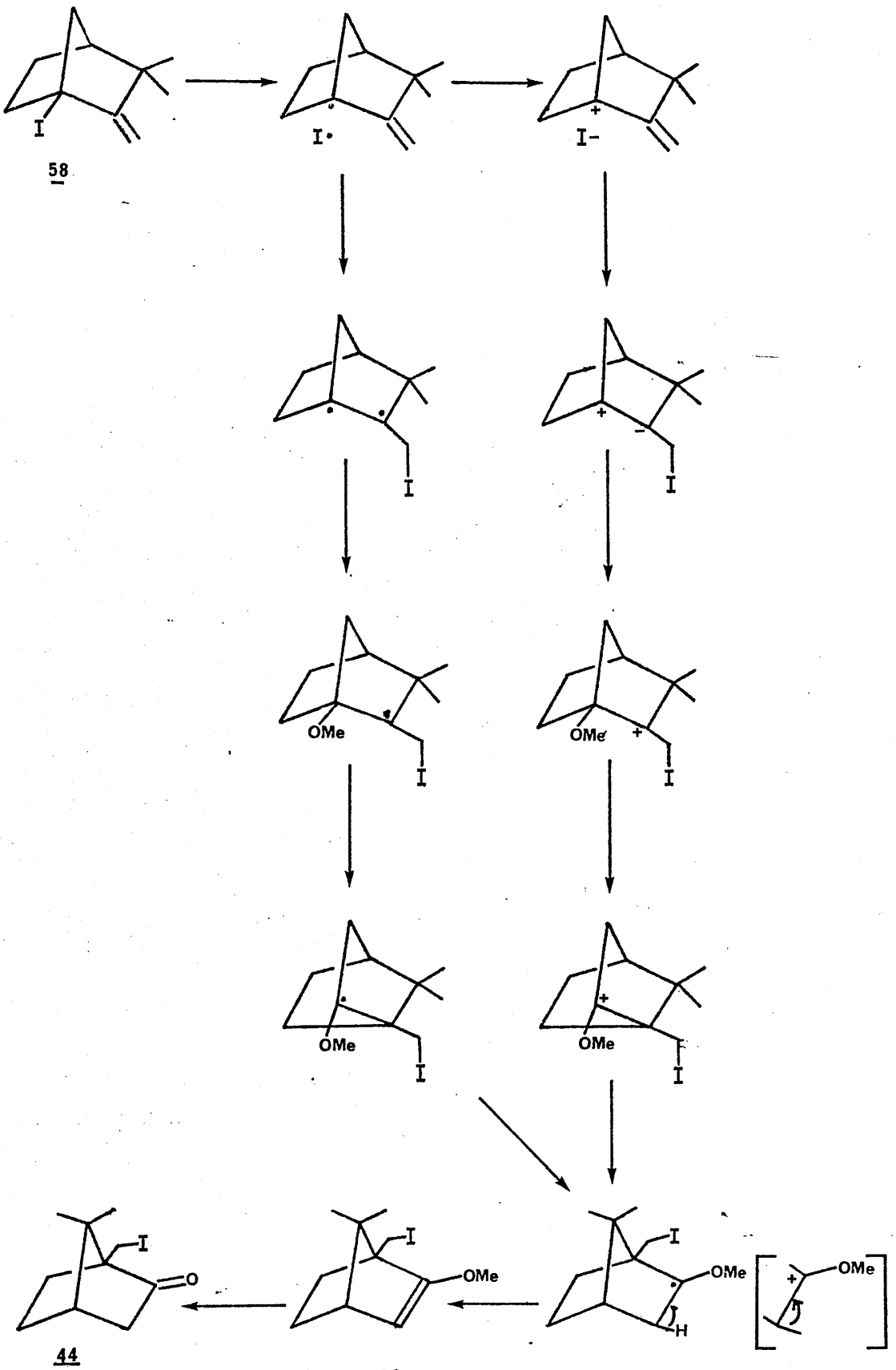
Figure 37

In practice, alkyl bromides yield almost exclusively radical products whereas analogous iodides give predominately ionic products and this difference is attributed to the relative rates of competing radical and ionic pathways in the two series. Since alkyl iodides have a low-lying $n \rightarrow \sigma^*$ transition with $\lambda_{max} \sim 260nm$, irradiations are most commonly carried out with a low-pressure mercury lamp which has its principle emission at 254 nm. Medium-pressure arcs are employed for both iodides and bromides where the absorption is markedly blue shifted with $\lambda_{max} \sim 210nm$.

Photolysis of 1-iodo camphene in methanol for 52 hours gave two major products; one was identified as starting material and the other as 10-iodo camphor 44, a known compound, which was thoroughly characterised by conversion to its oxime, a comparison sample of which was available. The isolation of 44 from the reaction mixture

has been rationalised in terms of either a radical[218] or an ionic process which involves an electron deficient species capable of rearrangement, a process not uncommon for similar bicyclic compounds. The proposed scheme is shown in figure 38.

The behaviour of this iodide is perhaps a result of the reaction conditions; a static system was employed whereby the irradiated solution was neither stirred nor agitated. The radical pair produced may therefore have an extended life-time, with the result that an intramolecular rearrangement, as shown, could occur. The higher percentage of ionic products recorded for both bromides and iodides in ethylene glycol is cited as evidence for a barrier to diffusion;[215] presumably, the viscous nature of the solvent militates against radical pair diffusion from the solvent cage and thus favours more electron transfer. Similarly, the intimacy of the radical pair in the present reaction would favour recombination, electron transfer and addition to the exocyclic double bond and disfavour nucleophilic trapping. Examples of rearrangements occurring under photolysis conditions are known;[219] irradiation of 1-iodomethylnorbornane 59 in methanol (Fig.39) afforded a mixture of bicyclo [2.2.2.] and bicyclo [3.2.1.] octyl ethers.[215] The identical reaction, repeated in pentane (non nucleophilic) gave the rearranged iodide which lends support to the proposed rationale regarding the photolysis and subsequent reaction of 1-iodo camphene.



58

44

Figure 38

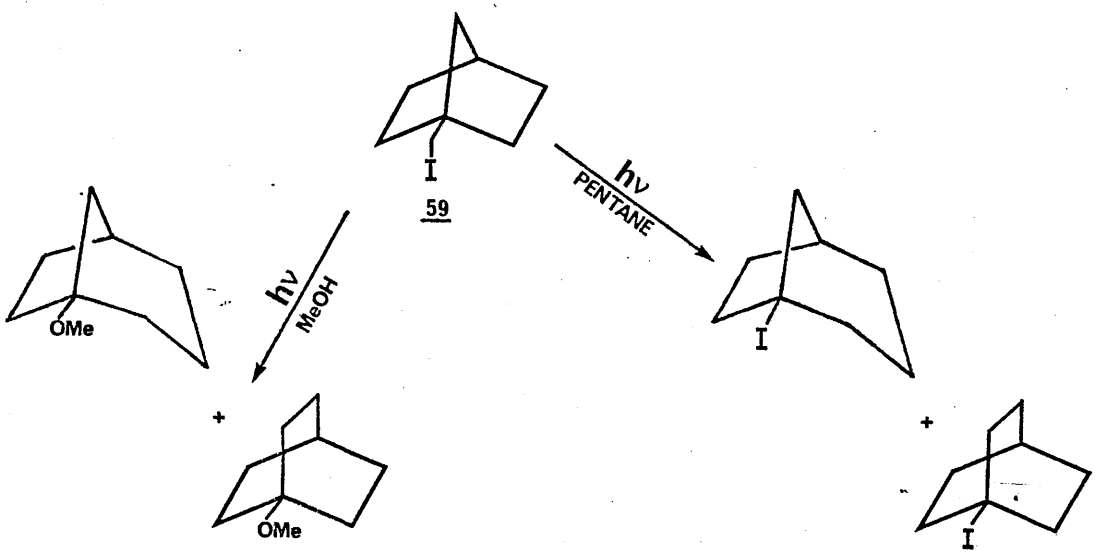


Figure 39

A reassessment of the design of the photochemical reactor resulted in a system which was both agitated and vented with a flow of argon. Employing this modified apparatus, a single product was obtained in ≃ 90% yield and in a much shorter reaction time. Analysis revealed that the unknown was camphor and its formation was envisaged as in Figure 40.

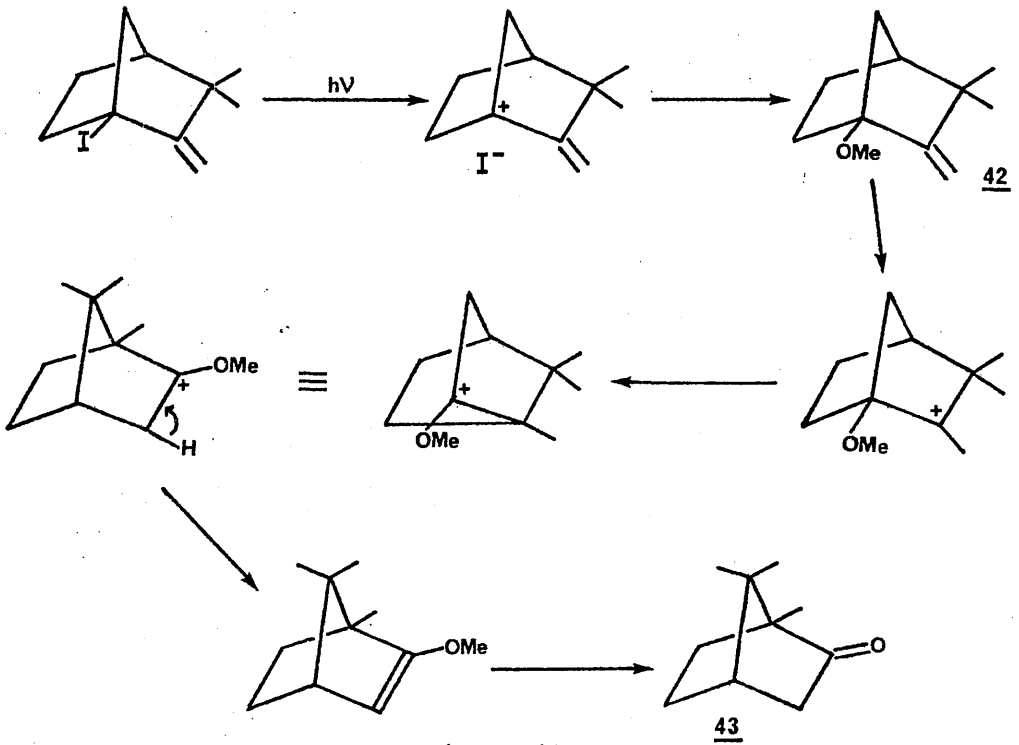
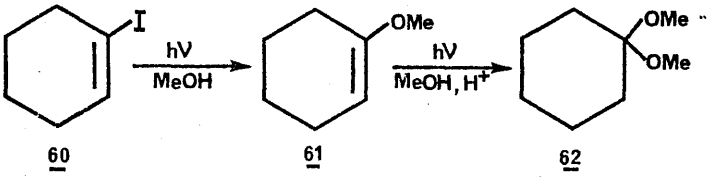


Figure 40

The conversion of 1-methoxy camphene 42 into camphor 43, via an acid-catalysed Wagner-Meerwein rearrangement as postulated above, bears remarkable similarities to the experiment carried out by McNeely and Kropp[220] which showed that irradiation of 1-iodocyclo-hexene 60, in methanol, and in the absence of an iodine scavenger, resulted in the formation of the ketal 62, via acid-



60 61 62

Figure 41

catalysed addition of methanol to the enol ether. However, in the presence of zinc, the major product formed in the latter example is the enol ether 61 and, similarly, 1-methoxy camphene 42 is isolated exclusively in the former reaction.

Confirmation of the existence of an acid-catalysed Wagner-Meerwein rearrangement came later, when, in an attempt to convert the photolysis-derived 1-methoxy camphene into the corresponding 4-substituted bornanone with trichloroacetic acid, only camphor was recovered (Fig. 42); this result indicated the enhanced stability of carbonium ion (1) compared to (2) and its ultimate decomposition to camphor.

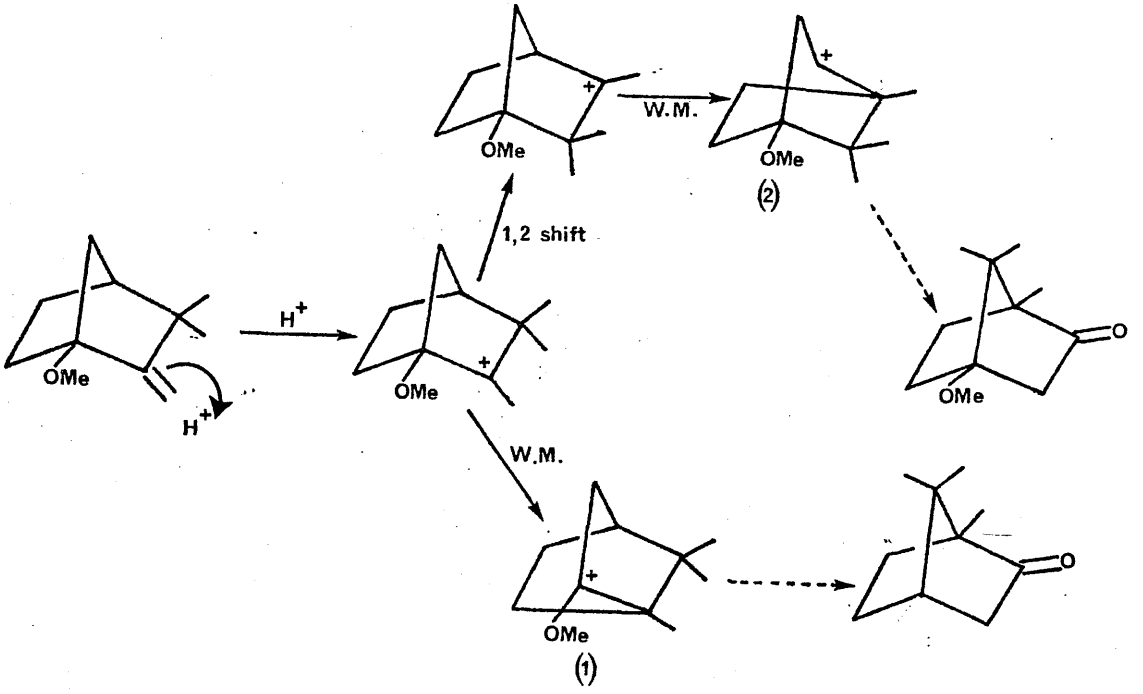
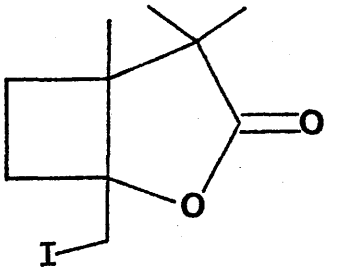


Figure 42

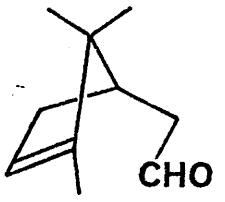
Photolysis of 4-iodo camphor 20 in the original photochemical reactor gave the desired product 22 in very low yield; the major product was thoroughly characterised and found to be a novel lactone 46.



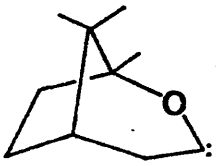
46

The solution photochemistry of camphor is well documented,[221-223] the major product being α-campholenic aldehyde 63. Evidently, 46 is a complex photo-product derived perhaps from the combined excitation of the carbon-halogen bond and the carbonyl moiety. A possible precursor of the lactone is an oxycarbene 64 analogous to

the type known to be generated in the photolysis of camphor[223] and which is trapped as an enol ether and an acetal.



63



64

This phenomenon of photochemical ring expansion via cyclic oxycarbenes is not limited to camphor but is known to occur in other cyclic ketones.[224] Yates and Kilmurry[225] found that irradiation of cyclocamphanone 65 in methanol, gave the ring-expanded cyclic acetal 66 and the experiment repeated in the presence of air, afforded the lactone 67 (Fig. 43). The

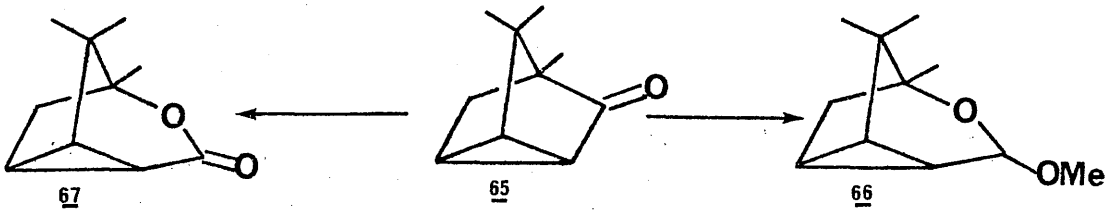
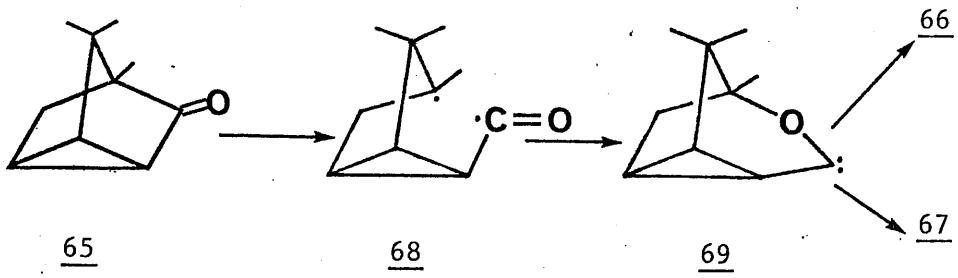


Figure 43

transformation is considered to proceed via carbonyl excitation followed by α-cleavage to give the bi-radical 68; the oxycarbene is formed by ring closure at the oxygen, and this species reacts

with solvent or air to give the acetal or lactone respectively.



65 68 69

Figure 44

ANISOCHRONY

As long ago as 1957,[226] it had been noted that geminal nuclei in compounds of the ethane type, exemplified by ClBrFC*CF_2Br, where * denotes a chiral carbon, exhibited chemical shift non-equivalence even at high temperature. Diastereotopism in prochiral methylene hydrogens was also observed for many systems including the ethyl group of esters[227] and sulphoxides,[228] where the vicinal chiral group induced magnetic non-equivalence of the protons resulting in an AB quartet splitting pattern. The origin of such an effect was commonly ascribed to the existence of preferred conformers of the methylene or isopropyl (another common sensor group) groups with respect to the asymmetric centre[229,230] (Fig. 45).

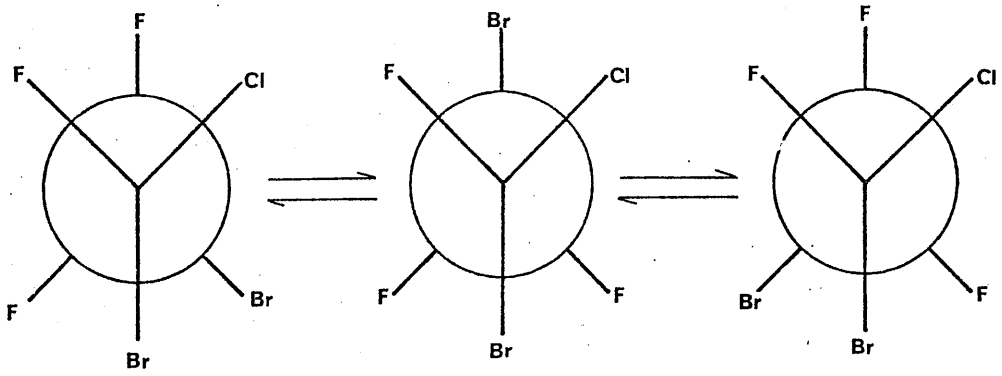


Figure 45

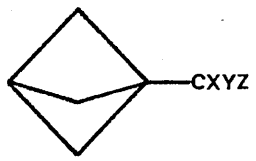
However, other workers suggested that a symmetry argument, completely independent of any conformational preference, could equally account for the observed diastereotopism.[231] The observed effect $\Delta\delta_{obs}$ would therefore be a combination of the two effects, the conformer

population independent (intrinsic) term $\Delta\delta_i$ and the population dependent term, $\Delta\delta_c$.

Gutowsky pointed out that it was feasible in practice to partition the time-averaged chemical shift difference (anisochrony) into these two terms[232] and great interest has centred round the attempts to evaluate the relative importance of the two components.

It is logically impossible to construct molecules or employ experimental conditions that will exhibit only conformational but not intrinsic anisochronism for geminal groups; however the converse is not true.[233] A method first applied by Raban[234] to measure the intrinsic contribution relied on low temperature N.M.R. where rotation about carbon-carbon single bonds in ethane type compounds was slow on the experimental time-scale resulting in observation of each individual rotamer.

An alternative approach was suggested by Mislow and Raban,[235] in which conformational homogeneity was accomplished by molecular symmetry; the diastereotopism of the cyclic methylene hydrogens in compounds of type 70 is due solely to the asymmetry of their



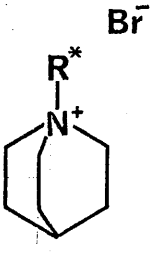
70

environment, since the three fold rotational symmetry present, produces conformers of equal population. In the basic structural type $\left[R^{*} \right] CU_2V$ (where CU_2V is the sensor part of the molecule and

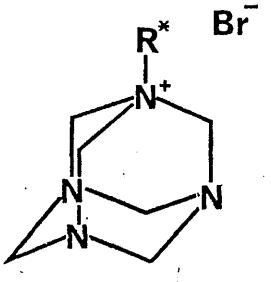
[R^*] is the chiral perturber group), the symmetry element mentioned above, can be incorporated in the moiety containing the sensor group, that containing the chiral perturber group or both. Examples of the last class are not known, but several of the preceding types do exist. The requirements for such classes of compound are as follows:

'The molecule must contain two structural moieties of such a nature that, when joined together by a single bond, there exists the possibility of three-fold degenerate rotation about this bond. One of the moieties must be chiral by itself and the other must contain two groups of sensor nuclei that are enantiotopic in the absence of the chiral moiety.' [235]

The first class of molecule, represented by $XYZCC(CU_2V)_3$, is exemplified by the quaternary salts 71 and 73, prepared from quinuclidine or hexamine with suitable chiral alkylating agents.[236]



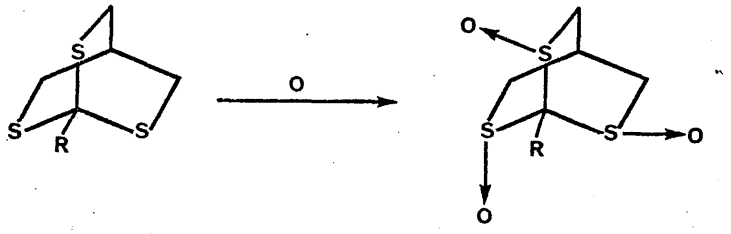
71



73

The geminal ring-methylene protons adjacent to the positive nitrogen give rise to an AB quartet at room temperature which can only be due to intrinsic anisochrony. Further examples of this class employed similar rigid cyclic systems with chiral bridgehead substituents.[233, 237, 238.]

A novel propeller-shaped compound 74 obtained by controlled oxidation of derivatives of the 2, 6, 7 - trithia bicyclo [2,2,2] octane system 75 is an example of the second class of molecule ($R_3^*CCU_2V$) in which the symmetry element is present in the chiral perturber, and R contains an acyclic prochiral moiety.[233,237].



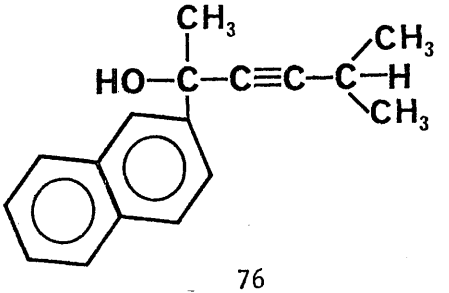
75 74

When a benzyl substituent is attached (R = $-CH_2Ph$) the methylene protons are isochronous, but anisochronous when R is dimethyl or di(trifluoromethyl) carbinol.

The two classes differ in that in the former the time averaged chemical shift difference is equal to six different chemical shifts for the sensor nuclei in a frozen conformer; these average to two under rapid rotation while in the latter it is equal to the chemical shift difference in each of the three stable conformations.[239]

In 1966, Synder proposed[240] that an unambiguous test for the origin of magnetic non-equivalence would seem to reside in the examination of the N.M.R. spectrum of compounds of the type $[R^*]\ C\ (C{\equiv}C)_m\ CU_2V$ and $R_3^*C(C{\equiv}C)_m\ CU_2V$. Assuming that the barrier to rotation of substituents attached to an acetylenic linkage is low, then the energy difference between the conformers is negligible.

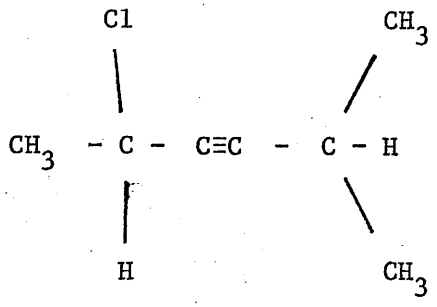
Consequently, if magnetic non-equivalence is observed in this class, it must be due to magnetic asymmetry. In theory, a state of barrier-free rotation should be reached, as the number of triple bonds increases, but since this necessitates the presence of local $C_{\infty v}$ symmetry in one of the attached groups, this limit is unattainable.[239] In a study employing self-consistent molecular orbital theory to estimate the internal rotation of a series of hydrocarbons[241] it was found that the torsional barrier for the two methyl groups in 2-butyne (dimethylacetylene) was approximately 5 cal mol^{-1}, which compared well with previous thermodynamic[242] and infrared[243] investigations on the system and a microwave determination[244] for the related structure, methylsilyl acetylene, which had a barrier of 3 cal mol^{-1}. Compounds of the type mentioned, incorporating an acetylenic bond, $R^{*}C(C{\equiv}C)CU_2V$ have been synthesised and have met with some success. Mislow et al[239] prepared 2-(2 naphthyl)-5-methylhex-3-yn-2-ol 76 and found that it



76

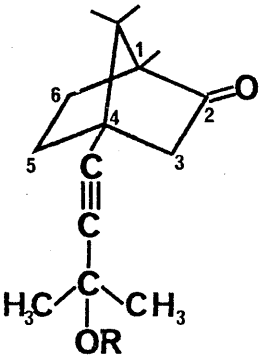
exhibited two methyl doublets in the 300-MHz ^{1}H N.M.R. spectrum in pyridine at ambient temperature, $\Delta\delta$ = 0.0013 ppm. An earlier attempt by Ejchart et al[245] to observe proton anisochrony was unsuccessful probably because the spectral dispersion of protons (typically a range of 1 - 15 ppm.) is an order of magnitude smaller than that for carbon

(1 - 200 ppm.), resulting in a sensor nucleus which requires a larger magnetic field to counteract the inherent insensitivity. As a consequence of this, Stiles and Jones[246] studied the ^{13}C N.M.R. of 2-Chloro-5-methylhex-3-yne 77 and observed geminal anisochrony with a chemical shift difference, $\Delta\delta$ of 0.011 ppm.



77

It was decided to synthesis a compound of the type $R^{*}C(C{\equiv}C),CU_2V$ where the chiral perturber group was the bicyclic skeleton of camphor and whose chirality was induced by the difference in substitution pattern at C(2) and C(6); the more remote asymmetry afforded by this system is in marked contrast to that in 76 and 77 which carried heteroatoms at the chiral carbon. It may be noted that, besides the chiral centre at the C(4) bridgehead position, there exists another asymmetric carbon at C(1), but its influence on the geminal methyl groups must be, due to its remoteness, slight.



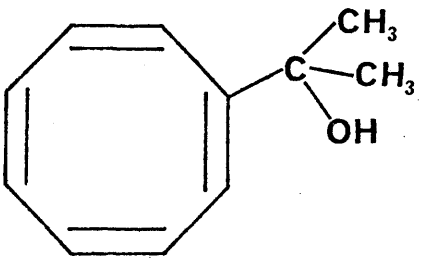
39 R = H

40 R = $\overset{O}{\overset{\|}{C}}-CH_3$

41 R = Me.

A result of the synethetic method employed to prepare compounds 39, 40 and 41 (see experimental section and scheme 1) is the uncertain optical purity of the end products, but this is inconsequential since when the bicyclic skeleton is in the other enantiomeric form, the roles of the geminal methyl groups are reversed.

Although preparative constraints dictated the use of dimethyl carbinol as the sensor group in compound 39, previous work in this field had employed this moiety; the anisochronous geminal methyls in the group had been used to study the cyclooctatetraene ring reversal in 78 by dynamic N.M.R. methods.[247] Similarly,

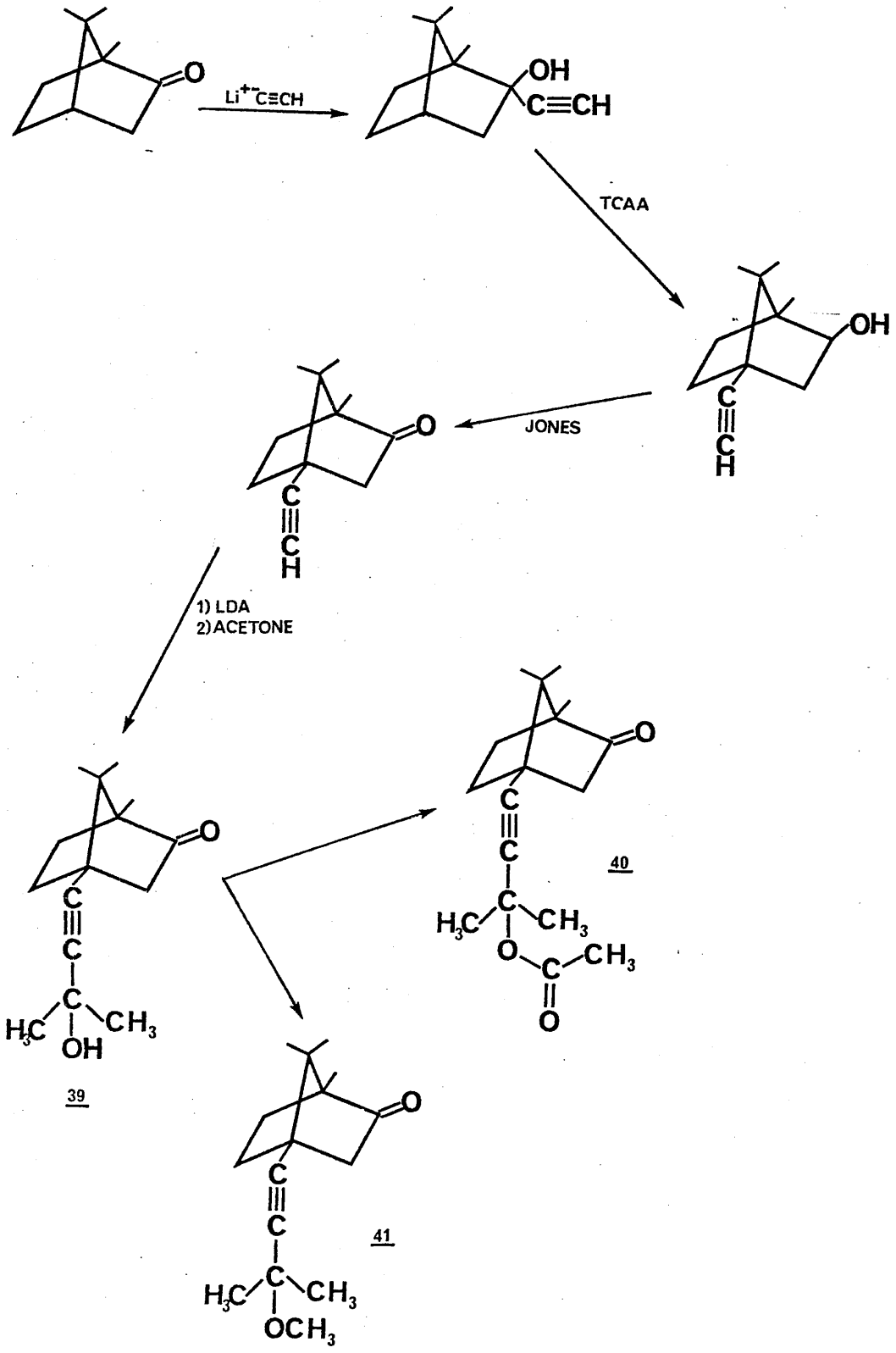


78

the propeller molecule, synthesised by Binsch and Franzen,[233,237] as an example of the $R^{*}_{3}CCU_{2}V$ class employed dimethylcarbinol as one of the sensor groups.

Proton decoupled ^{13}C N.M.R. spectra of the alcohol 39, and its acetate 40, (Table 11) at ambient temperature, ca 30°, showed a small but distinct separation of the signals for the two geminal methyl groups under conditions of higher resolution incorporating more closely spaced data points; these chemical shift differences $\Delta\delta$ were 0.012 and 0.013 ppm. respectively and are accurate to ±0.002 ppm. In contrast, the methyl ether 41, showed no anisochrony; in view of the results for the closely related alcohol and acetate compounds the anomalous behaviour of the ether is most probably due to accidental magnetic equivalence of the geminal methyl groups.

As noted earlier, employing an ethynylic moiety in the molecule eliminates conformational preferences since it is assumed that the barrie to rotation around the acetylenic linkage is small, as is the case for dimethylacetylene. In the present system, it seems reasonable to presume that the torsional barrier is low and perhaps, because of the 'tied back' nature of the ring carbon bond angles at C(4), even less than the methyl substituted ethyne. In comparison, the geometry of the substituted hexyne studied by Mislow et al[239] suggests that the barrier in this example may be higher; the large naphthyl derivative could quite conceivably influence the conformations in the molecule, resulting in anisochrony induced by chirality and rotamer preference.


O
Li+ -C≡CH
OH
C≡CH
TCAA
OH
C
≡
CH
JONES
O
C
≡
CH
1) LDA
2) ACETONE
O
C
≡
C
H3C
CH3
OH
39
O
C
≡
C
C
H3C
CH3
O
C
CH3
O
40
O
C
≡
C
C
H3C
CH3
OCH3
41

SCHEME 1

TABLE 11

^{13}C CHEMICAL SHIFT (PPM.) OF ALCOHOL 39, ACETATE 40 AND METHYL ETHER 41.

COMPOUND	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)*	C(12)*	C(13)	C(14)	C(15)	C(16)
39	58.3	216.5	48.3	43.6	33.9	29.2	50.4	18.2	16.8	10.0	88.7	81.2	65.1	31.9		
40	58.2	216.2	48.1	43.6	33.7	29.4	50.6	18.1	16.7	10.0	84.6	83.6	72.2	29.4	169.05	22.0
41	58.2	216.1	48.4	43.7	34.0	29.2	50.4	18.2	16.9	10.0	85.2	83.6	70.6	28.7	51.4	

C(15) and C(16) for compound 40 correspond to the acetate carbonyl and methyl respectively.
C(15) of compound 41 is assigned to the ether methyl.
Assignments indicated by * may be reversed.

HYPERVALENT IODINE COMPOUNDS

Although alkyl iodides are normally inert to the more common oxidising agents such as ozone, periodate and hydrogen peroxide,[248] they are readily oxidised by peracids.[189,248,249] Several workers have reported that various peroxy acids, particularly meta-chloroperbenzoic acid[248,189] and peracetic acid,[249] yield oxidative displacement products on reaction with alkyl iodides. This is in marked contrast with aromatic iodides which afford iodo dicarboxylates under analogous conditions;[251] hydrolysis of these di-esters, with base, yields iodoso compounds[252] (Fig.46).

$$PhI + 2CH_3COOOH \longrightarrow PhI(OAc)_2 \xrightarrow{+\bar{O}H} PhIO.$$

Figure 46

It has been suggested that the oxidation of alkyl iodides by peracids proceeds via the alkyl iodoso compound (transitory intermediate) which subsequently rearranges to a hypoiodite;[248] conjugation with an aromatic ring is a prerequisite for the stability of an I-O bond,[253] a factor which is absent in aliphatic substrates and which could explain the momentary existence of an iodoso alkane. Nevertheless, alkyl iodoso compounds have been synthesised which incorporate double bonds that probably act in a similar, but less efficient manner than the aromatic rings of the corresponding aryl iodoso compounds.[254] Reich and Peake[248] have

recently postulated that the iodoso-hypoiodite rearrangement proposed for the oxidation of alkyl iodide substrates involves either an ion-pair or radical pair intermediate as shown in Figure 47. The ease with which the carbon-iodine bond is cleaved

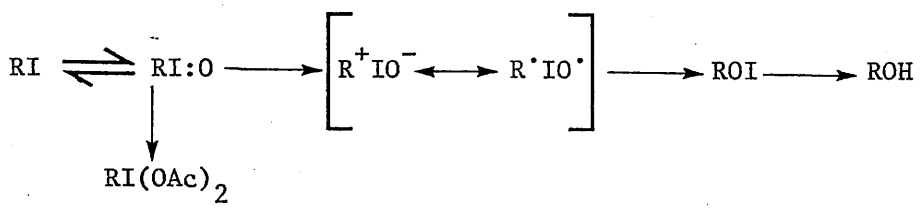


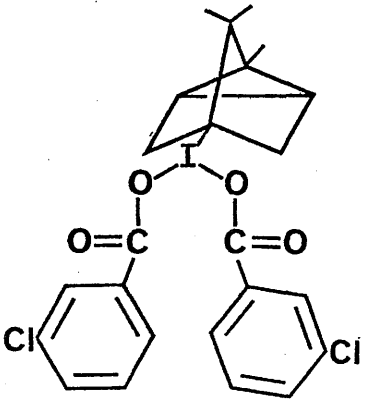
Figure 47

appears to be a dominant factor in determining the course of the reaction; if a carbonium ion can be generated on R, then presumably an oxidative displacement will take place leading to the alcohol or olefin. However, if the opportunity to create a carbonium ion is minimised, then the iodoso species may be trapped as an iodo-dicarboxylate, analogous to aryl iodides.

It was felt that an investigation of the reaction was warranted and, in particular, the result of oxidising an alkyl iodide, substituted at a relatively inert position was considered to be of some interest. Recently, 1-adamantyl iodide was oxidised with m-chloroperbenzoic acid to adamantan-1-ol;[255] the bridged ring system results in a diminution in the reactivity of the substituted carbon by a factor of 1000 compared with an acyclic derivative, but clearly this is insufficient to deter the formation of a carbocation.[256] The reactivity of the bridgehead position in various bicyclic and polycyclic compounds is known to decrease along the series:

adamantyl > norbornyl > tricyclyl > triptycyl; 1-bromo norbornane yields the 1-hydroxy derivative only after treatment with aqueous silver nitrate at 150° for 2 days. In the light of these facts, it was decided to attempt the synthesis of 4-iodo tricyclene 47, whose bridgehead reactivity is a factor of ca 10^{15} less than that of 1-adamantyl iodide[256] and consequently less prone to forming a bridgehead carbocation.

The tricyclic system was prepared from 4-iodo camphor tosyl hydrazone via the Bamford-Stevens reaction and purified by column chromatography on alumina. The reaction of 47 with m-chloroperbenzoic acid in methylene chloride afforded a crude sample of the dicarboxylate, iodoso tricyclene di-meta-chlorobenzoate 48; attempted purification by preparative t.l.c. afforded 47 and m-chlorobenzoic acid, indicative of di-ester decomposition. Recrystallisation from toluene gave a pure sample of the di-benzoate 48. Characterisation of this compound

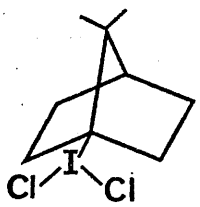


48

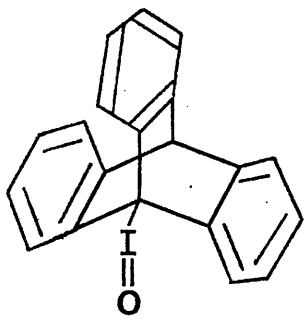
was aided by the ^{13}C spectrum shown on Table 12; in accord with other iodinanes (tricoordinate iodine compounds),[258] there is a striking

downfield shift of the carbon α to iodine relative to the same carbon in the monovalent precursor. In the present example, this amounts to a deshielding effect of 36.39 ppm. attributed primarily to the change in oxidation state of the iodine. The two distinct β-carbons of the tricyclic skeleton, C(3) and C(7) experience small shielding and deshielding effects respectively with respect to the parent iodide 47, suggesting a more complex interaction at these positions, including probably, steric factors.

Hydrolysis of 48 with sodium hydroxide consistently gave iodo tricyclene 47 (ca 50%) and m-chlorobenzoic acid. Clearly these two compounds alone did not complete the material balance, but repeated extractions failed to yield the missing product. The inability to prepare the iodoso compound is in agreement with the findings of Roberts and Dence[257] who reported that the base catalysed hydrolysis of the dichoride of iodoapocamphane 79 failed to give an iodoso product. In addition, they noted that the potentially unreactive substrate, iodo tryptycene could not be chlorinated to form a possible precursor to iodoso tryptycene 80; this behaviour was explained in terms of steric hindrance about the iodine atom.



79



80

The failure of precursors 48 and 79 to yield iodoso products under hydrolysis conditions is perhaps a result of the structure of these two substrates; the alkyl hydrocarbon skeletons lack unsaturation, which has been proposed as essential to I-O bond stabilisation, and hence the inherently unstable 4-iodoso tricyclene disproportionates immediately to the iodo and iodoxy hydrocarbon. The choice of alkyl iodide has eliminated the possibility of oxidative displacement taking place under reaction conditions, as evidenced by the isolation of 48, which is probably generated via the iodoso compound which is subsequently trapped as the dicarboxylate. Thus it seems likely that in the reaction sequence between 47 and recovering 4-iodo-tricyclene from the unsuccessful hydrolysis of 48, the iodoso compound is formed twice, but is either captured or disproportionates; the existence of the trapped di-benzoate species suggests that the disproportionation is slow with respect to the trapping process.

Results from the present work suggest that disproportionation has occurred after hydrolysis, but no iodoxy tricyclene was recovered; presumably this compound will be extremely polar and hence have a tendency to remain on silica or in the aqueous phase. The case for disproportionation is further strengthened when it is considered that the more stable aryl iodoso compounds themselves disproportionate, albeit at a much slower rate than is envisaged for the present compound.

Thus, despite the lack of success in obtaining an iodoso

alkane, it has been shown that by careful choice of the alkyl substrate, namely its inertness at the iodine-substituted carbon, alkyl iodides can be made to react in a similar fashion to aryl iodides, on treatment with peracids.

TABLE 12

^{13}C CHEMICAL SHIFTS (ppm.) OF 47 AND 48.

COMPOUND	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)
47	23.74	20.55	43.40	43.90	43.40	20.55	47.34	19.52	19.52	11.77
48	23.85	20.00	38.26	80.29	38.26	20.00	48.95	19.67	19.67	11.55

For 48, the aromatic ring carbons absorb between 128.12 - 134.34 ppm. and the carbonyl carbon of the benzoate at 169.41 ppm.

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